IN THE MATTER OF

STERLING DRUG, INC., ET AL.

FINAL ORDER, OPINION, ETC., IN REGARD TO ALLEGED VIOLATION OF SECS. 5 AND 12 OF THE FEDERAL TRADE COMMISSION ACT

Docket 8919. Complaint, Feb. 23, 1973—Final Order, July 5, 1983

This order requires a New York City manufacturer of nonprescription drug products, among other things, to cease advertising that "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol" or any other nonprescription internal analgesic has been proven to be superior to other pain relieving products, unless such claim has been substantiated by two well-controlled clinical tests. The company must have a reasonable basis to support any claim that its pain relievers are therapeutically superior to others, as well as competent and reliable scientific evidence for representations that the comparative pharmaceutical qualities of its analgesics have been proven or established. The order further prohibits the manufacturer from advertising that its products contain any unusual or special ingredient, when in fact such ingredient is commonly used in similar products; or from making any claim which misrepresents the product's analgesic ingredient.

Appearances

For the Commission: *Joel N. Brewer, Randell C. Ogg, Teresa A. Hennessy, Leslie E. Rossen* and *Roberta Gross.*

For the respondents: *Lionel Kestenbaum, Norman G. Knopf, William D. Appler, Jeffrey L. Kestler, Amanda B. Pedersen* and *Susan S. Pecaro, Bergson, Borkland, Margolis & Adler,* Washington, D.C.

COMPLAINT

Pursuant to the provisions of the Federal Trade Commission Act, and by virtue of the authority vested in it by said Act, the Federal Trade Commission, having reason to believe that Sterling Drug, Inc., a corporation, Dancer-Fitzgerald-Sample, Inc., a corporation, and Lois Holland Callaway, Inc., a corporation, hereinafter referred to as respondents, have violated the provisions of said Act, and it appearing to the Commission that a proceeding by it in respect thereof would be in the public interest, hereby issues its complaint stating its charges in that respect as follows:

PARAGRAPH 1. For purposes of this complaint the following definitions shall apply:

1. *Commerce* means commerce as defined in the Federal Trade Commission Act.

2. *False advertisement* means false advertisement as defined in the Federal Trade Commission Act.

PAR. 2. Respondent Sterling Drug, Inc., is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware with its office and principal place of business located at 90 Park Avenue in the City of New York, State of New York. [2]

Respondent Dancer-Fitzgerald-Sample, Inc., is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware with its office and principal place of business located at 347 Madison Avenue, in the City of New York, State of New York.

Respondent Lois Holland Callaway, Inc., is a corporation organized, existing and doing business under and by virtue of the laws of the State of New York with its office and principal place of business located at 745 Fifth Avenue, in the City of New York, State of New York.

PAR. 3. Respondent Sterling Drug, Inc., is now and has been for all times relevant to this complaint engaged in the manufacturing, advertising, offering for sale, sale and distribution of certain non-prescription internal analgesic preparations which come within the classification of drugs as the term "drug" is defined in the Federal Trade Commission Act. The designations, directions for use and active ingredients for some of these analgesic drugs are as follows:

1. Designation: "Bayer Aspirin"

   Active ingredients:

   Aspirin
   Dosage: 1 or 2 tablets with water every 4 hours, as necessary, up to 12 tablets a day.

2. Designation: "Bayer Children's Aspirin"

   Active Ingredients:

   Aspirin
   Dosage: Varies depending upon age of child.

3. Designation: "Cope"

   Active Ingredients:

   Aspirin
   Caffeine [3]
   Methapyrilene Fumarate
   Magnesium Hydroxide
   Aluminum Hydroxide (Dried Gel)
   Dosage: 1 or 2 tablets every 4 hours, as needed, up to 9 tablets per day.

4. Designation: "Vanquish"

Active Ingredients:

Aspirin
Caffeine
Acetaminophen
Magnesium Hydroxide
Aluminum Hydroxide (Dried Gel)
Dosage: 2 caplets with water. Can be repeated every 4 hours if needed, up to 12 caplets per day.

5. Designation: "Midol"

Active Ingredients:

Aspirin
Caffeine
Cinnamedrine HCL
Dosage: 2 Midol Tablets with water. Repeat 1 or 2 tablets every 4 hours as needed, up to 8 tablets per day.

PAR. 4. Respondent Dancer-Fitzgerald-Sample, Inc., is now and for all times relevant to this complaint has been an advertising agency of Sterling Drug, Inc., and for all times relevant to this complaint, has prepared and placed for publication, advertising material, including but not limited to the advertising referred to herein, to promote the sale of the said "Bayer Aspirin", "Bayer Children's Aspirin" and "Cope".

Respondent Lois Holland Callaway, Inc., for all time relevant to this complaint has been an advertising agency of Sterling Drug, Inc., and for all times relevant to this complaint, has prepared and placed for publication advertising material, including but not limited to the advertising referred to herein, to promote the sale [4] of the said "Vanquish".

PAR. 5. In the course and conduct of its aforesaid business, respondent Sterling Drug, Inc., causes the said analgesic drug preparations, when sold, to be transported from its places of business located in various States of the United States to purchasers thereof located in various other States of the United States and in the District of Columbia. Respondent Sterling Drug, Inc., maintains and at all times relevant to this complaint has maintained, a substantial course of trade in said preparations in commerce. The volume of business in such commerce has been and is substantial.

PAR. 6. In the course and conduct of their businesses, respondents Sterling Drug, Inc., Dancer-Fitzgerald-Sample, Inc., and Lois Holland Callaway, Inc., have disseminated, and caused the dissemination of, certain advertisements concerning the said drugs by the United States mail and by various means in commerce, including but not limited to, advertisements inserted in magazines and newspapers,

and by means of television and radio broadcasts transmitted by television and radio stations located in various States of the United States, and in the District of Columbia, having sufficient power to carry such broadcasts across state lines, for the purpose of inducing and which were likely to induce, directly or indirectly, the purchase of said drugs and have disseminated, and caused the dissemination of, advertisements concerning said drugs by various means, including but not limited to the aforesaid media, for the purpose of inducing and which were likely to induce, directly or indirectly, the purchase of said drugs in commerce.

PAR. 7. Typical of the statements and representations made in the advertisements, but not all inclusive thereof, are the following:

A. For Bayer Aspirin:

(1) To relieve a headache fast Bayer Aspirin's got the best help there is. Of all the leading pain relievers you see advertised, only Bayer is 100% aspirin. And Aspirin is what doctors recommend. [5]

(2) I'm Ozzie Nelson. Here's something I'm passing along to *my* family. This booklet about pain relievers. Bayer tested its aspirin for quality against 220 other brands. The results? Bayer is superior. I also read about the latest report written by the American Medical Association Council on Drugs . . . Straight aspirin is preferred over other non-prescription pain relievers. Find out why . . . aspirin's the best pain reliever. And Bayer's the best aspirin.

(3) Has anyone ever improved on Bayer Aspirin? Made a faster Aspirin? A more effective Aspirin? Lots of people have tried. They took plain Aspirin. Made it bigger. Smaller. They buffered it. They added extra ingredients. They squeezed it. Squared it. Flavored it. Gummed it. Capsuled it. Fizzed it. Even tried spraying it . . . They did everything—but improve it. Today there is still nothing faster . . . nothing more effective . . . than good old genuine Bayer Aspirin. It's pure Aspirin . . . not part Aspirin. It works wonders for headache, muscle pain, aches and fever of a cold. For just about anything that hurts.

(4) Would you like to see the inside story on all the major pain relievers you see advertised? Inside every single leading pain reliever is the same major ingredient . . . Aspirin . . . every one of those products relies chiefly on Aspirin. Surprised? Don't be . . . after all, Aspirin is the only pain reliever doctors overwhelmingly recommend for nearly every type of ache or pain. And did you know that Bayer is the only one of those pain relievers that makes all its own Aspirin? With care and experience no one else can match? That's why pure Bayer Aspirin, without Bufferin or Caffeine or any other extra ingredient is the pain reliever for you.

(5) Deciding which pain reliever you should take can be like a game. Some talk about strength, some talk about speed, some talk about ingredients they don't name. But of all the leading pain relievers you see advertised, Bayer is the only one that is all Aspirin. And Aspirin is what doctors recommend. [6]

(6) Bayer wants you to *know* about pain relievers . . . did you know that two Bayer Aspirin tablets bring all the pain relief power a headache can use? Did you know that Bayer without any additives is every bit as fast and effective in relieving pain as those products that have additives?

(7) Confused by claims? By shapes and sizes? By strange sounding ingredients? When you need fast relief from headache pain, don't forget this fact . . . Bayer is 100% Aspirin

and Aspirin is the strongest pain reliever you can buy. No wonder Bayer works wonders.

(8) If you've ever heard that all aspirin's alike, here's something you should know. While it's true that the United States Pharmacopoeia does set standards for aspirin, Bayer surpasses these standards in many ways. For example, Bayer standards require complete tablet disintegration within thirty seconds. That's ten times faster than the accepted five-minute standard. It's one of the things that helps make Bayer fast and gentle.

(9) 1ST MAN: How come Bayer doesn't buffer its aspirin? BAYER MAN: There's really no need to. In relieving pain, buffered aspirin isn't any faster or gentler than Bayer. Yes.

(10) When hot weather makes you feel headachy, tense, irritable, two Bayer Aspirin and a short rest can help you feel better fast!

It happens to most of us on a hot, humid summer day, when the pressures of daily living mount up. By mid-afternoon we feel so headachy and edgy that the simplest chore, the smallest disturbance becomes an irritation. We're in no mood to enjoy life or the company of others.

Here's how to turn that mood around: just take two Bayer Aspirin for your headache, sit down for a few minutes and relax. You too will say, "Bayer works wonders." These few minutes can make a world of difference in the way you feel and act. You'll enjoy being with people, and they'll enjoy being with you. [7]

Whenever you get headachy, tense and out of sorts on a hot summer afternoon, set aside a few minutes for Bayer Aspirin and a brief rest. Bayer is *pure* aspirin, not just *part* aspirin. Ask your pharmacist.

(11) Bayer recently tested its aspirin against 220 other brands. For purity, stability, speed of disintegration, Bayer was consistently better.

(12) I read about recent Bayer tests on aspirin. They tested for *quality,* for purity, for *freshness* against 220 other brands. The tests showed that Bayer makes the superior aspirin.

B. Bayer Aspirin for Children:

. . . You don't settle for any children's aspirin. You want the best. You want Bayer because no one makes aspirin like Bayer. No one purifies aspirin like Bayer. No one protects Aspirin like Bayer.

C. For Cope:

(1) Important studies made at the world's leading headache clinic show that for relief of severe nervous tension headaches a combination of a pain reliever and a sedative provides greater relief than either medication alone. Of all the leading remedies you can buy for ordinary nervous tension headaches, only Cope combines a gentle relaxer with a powerful pain reliever for really effective relief. If you have chronic headaches, see your doctor. For the usual nervous tension headache get Cope.

(2) I get it on rainy days. I get it during rush hour. I get it when the boss looks over my shoulder. When the name of the pain is nervous tension headache, the name of the remedy is Cope. Because Cope gives you a powerful pain reliever plus a gentle relaxer. [8]

D. For Vanquish:

(1) (3 tablets are shown with 1 caplet of Vanquish)

For your headache pain, here are your major choices: This leading extra strength product has no buffers. This leading buffered product has no extra strength. This leading pain reliever has strength but no buffers. Of all the leading pain relievers you can buy, only Vanquish gives you extra strength and gentle buffers. Vanquish. The choice. (Sterling Drug, Inc.)

(2) When you get a headache we think you should take Vanquish. And we'll show you why in a head to head comparison. This is Vanquish. It gives you extra strength and gentle buffers. And its the only leading pain reliever that does. This is a leading extra strength product. It has no buffers. And there are no buffers in this other extra strength product either. This leading buffered product comes without extra strength. We think your headache deserves extra strength and you deserve gentle buffers. (Sterling Drug, Inc.)

(3) Vanquish is different. It gives you proven effectiveness of Aspirin as in this tablet plus extra medication as in these. But it also includes two gentle buffers . . . With Vanquish the only one. (Sterling Drug, Inc.)

(4) Her headache is killing me. When she gets a pain in the head, it can be a big pain to me, so I give her Vanquish. Vanquish is strong medicine. Vanquish contains more pain relievers than the largest selling extra strength tablet . . . and it has gentle buffers. How's your headache, dear? Dit Dit Dit Dah . . . Vanquish is strong medicine. (Sterling Drug, Inc., and Lois Holland Callaway, Inc.) [9]

E. For Midol:

(1) Live Your Life . . . Relieved of Menstrual Distress. In the modern life you lead, there come the calm times, too. Strolling hand in hand. Reading together. Talking together. These are the precious, serene moments. And you let nothing interfere. Not even functional menstrual distress. How? With Midol. Because MIDOL contains:

An exclusive anti-spasmodic that helps STOP CRAMPS

Medically-approved ingredients that RELIEVE HEADACHE, LOW BACKACHE . . . CALM JUMPY NERVES . . .

Plus a special mood-brightener that gives you a real lift . . . gets you through the trying pre-menstrual period feeling calm and comfortable.

PAR. 8. Through the use of these advertisements, and others similar thereto not specifically set out herein, it was represented directly or by implication:

A. By respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc., that it has been established that:

1. Bayer Aspirin is superior in terms of significant therapeutic effect to any other aspirin.

2. Bayer Children's Aspirin is superior in terms of significant therapeutic effect to any other children's aspirin.

3. A recommended dose of Cope is more effective for the relief of "nervous tension headache" pain than a recommended dose of any other non-prescription internal analgesic.

B. By respondent Sterling Drug, Inc., that it has been established that:

1. A recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin.

2. Because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any non-prescription internal analgesic not containing buffers. [10]

C. By respondents Sterling Drug, Inc. and Lois Holland Callaway, Inc., that a recommended dose of Vanquish is more effective for the relief of pain than the largest selling "extra strength" tablet.

PAR. 9. In truth and in fact, none of said representations has been established, for reasons including, but not limited to, the existence of a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of all such representations.

PAR. 10. Through the use of these advertisements, and others similar thereto not specifically set out herein, it was represented directly or by implication by respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc. that:

A. Bayer Aspirin is superior in terms of significant therapeutic effect to any other aspirin.

B. Bayer Children's Aspirin is superior in terms of significant therapeutic effect to any other children's aspirin.

PAR. 11. There existed, at the time of said representations, no reasonable basis for making the above representations, in that respondents lacked competent and reliable scientific evidence sufficient to support such representations.

PAR. 12. Through the use of these advertisements, and other similar thereto not specifically set out herein, it was represented directly or by implication:

A. By respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc., that a recommended dose of Cope is more effective for the relief of "nervous tension headache" pain than a recommended dose of any other non-prescription internal analgesic.

B. By respondent Sterling Drug, Inc., that:

1. A recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin.

2. Because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any non-prescription internal analgesic not containing buffers. [11]

C. By respondents Sterling Drug, Inc. and Lois Holland Callaway,

Inc., that a recommended dose of Vanquish is more effective for the relief of pain than the largest selling "extra strength" tablet.

PAR. 13. There existed, at the time of said representations, a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of such representations.

PAR. 14. Moreover, respondents made said representations without disclosing the existence of such a substantial question as to the validity of each representation. In light of the representations made, the existence of such a substantial question is a material fact, which, if known to consumers, would be likely to affect their consideration of whether or not to purchase such products. Thus, respondents have failed to disclose material facts.

PAR. 15. Through the use of the aforesaid advertisements and others similar thereto not specifically set out herein, it was represented directly or by implication:

A. By respondents Sterling Drug, Inc. and Dancer-Fitzgerald-Sample, Inc. that a recommended dose of Bayer Aspirin relieves nervous tension, anxiety and irritability and improves the user's mood.

B. By respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc. that a recommended dose of Cope relieves nervous tension, anxiety and irritability and will enable persons to cope with the ordinary stresses of everyday life.

C. By respondent Sterling Drug, Inc. that a recommended dose of Midol relieves nervous tension, stress, fatigue and depression and improves the user's mood.

PAR. 16. There existed at the time of said representations no reasonable basis for making the above representation in that respondents had no competent and reliable scientific evidence to support such representations.

PAR. 17. Through the use of the advertisements referred to in Paragraph Seven, sections (A) (2) (3) (4) (6) (7) and (9), (C), and (D) above it was represented directly or by implication: [12]

A. By respondents Sterling Drug, Inc., Dancer-Fitzgerald-Sample, Inc., that Bayer Aspirin is as effective for the relief of headache pain (including "nervous tension headache" pain) as, and will cause gastric discomfort no more frequently than, any other non-prescription internal analgesic, including Cope and Vanquish;

B. By respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc., that Cope is more effective for the relief of "nervous tension headache" pain than any other non-prescription internal analgesic, including Bayer Aspirin and Vanquish;

C. By respondent Sterling Drug, Inc., that Vanquish is more effec-

tive for the relief of headache pain than any aspirin, including Bayer Aspirin, and will cause less gastric discomfort than any non-buffered internal analgesic, including Bayer Aspirin.

The representations referred to sections (A), (B), and (C) above are mutually inconsistent. Respondents have made claims for a product that are inconsistent with contemporaneous claims for other products made by the same firm.

PAR. 18. Furthermore, in advertisements for Cope, respondents Sterling Drug, Inc., and Dancer-Fitzgerald-Sample, Inc. referred to the results of tests or studies and represented, directly or by implication, that such tests or studies prove the claim that a recommended dose of Cope is more effective for the relief of "nervous tension headaches" than recommended doses of all other non-prescription internal analgesics.

PAR. 19. In truth and in fact, the tests or studies referred to do not prove the claim that a recommended dose of Cope is more effective for the relief of "nervous tension headaches" than recommended doses of all other non-prescription internal analgesics.

PAR. 20. Through the use of the advertisements referred to in Paragraph Seven, Sections A(11) and (12), and other similar thereto not specifically set out herein, respondents Sterling Drug, Inc. and Dancer-Fitzgerald-Sample, Inc. represented, directly or indirectly, that Bayer Aspirin has been tested against 200 other brands of aspirin for quality, purity, freshness, stability, and speed of disintegration, and that the results of the tests demonstrated that Bayer Aspirin is qualitatively superior to all of the other brands tested in all respects, and therapeutically superior to all of the other brands tested. [13]

PAR. 21. In truth and in fact, the tests referred to do not demonstrate that Bayer Aspirin is qualitatively superior in all respects, including speed of disintegration, to all other aspirins tested. Moreover, these tests do not demonstrate that Bayer is therapeutically superior to all other brands because at the time of such representations there existed a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drug product, concerning the validity, significance or interpretation of such tests as related to such representation.

PAR. 22. Respondents Sterling Drug, Inc. and Dancer-Fitzgerald-Sample, Inc. represented directly or by implication that Cope contained a unique formula in that it alone among non-prescription headache remedies contained both a pain reliever and an ingredient with sedative properties. In truth and in fact the ingredients referred to are aspirin and methapyrilene, both of which were available for non-prescription use in Excedrin PM. Therefore, the advertisements re-

ferred to in Paragraph Seven (C)(1) were and are misleading in a material respect.

PAR. 23. Respondents Sterling Drug, Inc. and Lois Holland Callaway, Inc., marketed and advertised Vanquish without disclosing in the advertising for this product that it contains aspirin and caffeine. Aspirin and caffeine are well-known commonplace substances widely available in a variety of non-prescription products. Moreover, the use of aspirin or caffeine can be injurious to health and may cause undesirable side effects. Thus, respondents have failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products.

PAR. 24. Furthermore, respondents Sterling Drug, Inc. and Dancer-Fitzgerald-Sample, Inc. marketed and advertised Cope without disclosing in the advertising for this product that it contains aspirin and caffeine. Aspirin and caffeine are well-known commonplace substances widely available in a variety of non-prescription products. Moreover, the use of aspirin or caffeine can be injurious to health and may cause undesirable side effects. Thus, respondents have failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products. [14]

PAR. 25. Furthermore, respondent Sterling Drug, Inc. marketed and advertised Midol without disclosing in the advertising for this product that it contains aspirin and caffeine. Aspirin and caffeine are well-known commonplace substances widely available in a variety of non-prescription products. Moreover, the use of aspirin or caffeine can be injurious to health and may cause undesirable side effects. Thus, respondent has failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products.

PAR. 26. Furthermore, in advertisements for Midol, respondents Sterling Drug, Inc. and Thompson-Koch Company represented directly or by implication that the analgesic ingredients in Midol are other than ordinary aspirin and that the stimulant in Midol is other than caffeine.

PAR. 27. In truth and in fact, the analgesic ingredient in Midol is ordinary aspirin, and the stimulant in Midol is caffeine.

PAR. 28. The advertisements referred to in Paragraph Eight above were, and are, misleading in material respects, as alleged in Paragraphs Nine, Thirteen, Fourteen, Nineteen, Twenty-one, Twenty-two, Twenty-three, Twenty-four, Twenty-five, and Twenty-seven and constituted and now constitute false advertisements.

PAR. 29. The making of claims for a product that are inconsistent

with contemporaneous claims for other products made by the same firm, as alleged in Paragraph Seventeen above, and the making of representations as alleged in Paragraphs Eleven, Thirteen, Fourteen, and Sixteen, constituted and now constitute unfair or deceptive acts or practices in commerce.

PAR. 30. The use by respondents of the aforesaid deceptive statements, representations, or claims, and the dissemination of the aforesaid false advertisements has had and now has, the capacity and tendency to mislead members of the consuming public into the erroneous and mistaken belief that said statements, representations, or claims were and are true and into the purchase of substantial quantities of said drugs of respondent Sterling Drug, Inc. by reason of said erroneous and mistaken belief. **[15]**

PAR. 31. In the course and conduct of its aforesaid business, and at all times mentioned herein, respondent Sterling Drug, Inc. has been and now is in substantial competition in commerce, with corporations, firms and individuals in the sale of drug products of the general kind and nature as those sold by respondent.

In the course and conduct of its aforesaid business, and at all times mentioned herein, respondent Dancer-Fitzgerald-Sample, Inc. has been, and now is in substantial competition in commerce with other advertising agencies.

In the course and conduct of its aforesaid business, and at all times mentioned herein, respondent Lois Holland Callaway, Inc. has been, and now is in substantial competition in commerce with other advertising agencies.

PAR. 32. The aforesaid acts and practices of respondents, as herein alleged, including the dissemination of false advertisements, as aforesaid, were and are all to the prejudice and injury of the public and of respondents' competitors and constituted and now constitute unfair methods of competition in commerce and unfair or deceptive acts or practices in commerce, in violation of Sections 5 and 12 of the Federal Trade Commission Act.

INITIAL DECISION BY

MONTGOMERY K. HYUN, ADMINISTRATIVE LAW JUDGE

JANUARY 30, 1981

PRELIMINARY STATEMENT

On February 23, 1973, the Federal Trade Commission ("Commission") issued a complaint charging Sterling Drug Inc. ("Sterling"),

Dancer-Fitzgerald-Sample, Inc. ("DFS") and Lois Holland Callaway, Inc. ("LHC") with violations of Sections 5 and 12 of the Federal Trade Commission Act, as amended (15 U.S.C. 45 and 52) in connection with certain advertisements for Bayer Aspirin ("Bayer"), Bayer Children's Aspirin ("BCA"), Vanquish, Cope and Midol, all over-the-counter ("OTC") internal analgesic products. Similar complaints were issued on the same date against *Bristol-Myers Company et al.* (Docket No. 8917) [102 F.T.C. 21] and *American* [2] *Home Products Corporation* (Docket No. 8918) [98 F.T.C. 136], in connection with certain advertisements for certain OTC internal analgesic products marketed by these firms.

On May 9, 1973, respondents Sterling & DFS filed their respective answers and LHC filed its answer on May 19, 1973, each denying that it violated the Federal Trade Commission Act. Administrative Law Judge William K. Jackson, originally assigned to this proceeding, entered a Prehearing Order, dated October 3, 1973, setting forth the issues of fact and law to govern the adjudicatory proceeding. This case, along with the two analgesic cases referred to above, was assigned to me upon Judge Jackson's retirement, effective January 1, 1975.

The parties were allowed extensive pretrial discovery. Numerous prehearing conferences were held in order to simplify the issues, to resolve disputes related to discovery and generally to expedite the trial preparation in this case.

Joint hearings in the three analgesic cases were held from June 6 through August 1, 1977. A number of complaint counsel's witnesses common to the three cases testified as to the design and execution of various surveys and studies upon which complaint counsel sought to rely. Some 66 exhibits were received in evidence and the transcript of the joint hearings comprised some 2850 pages. The joint hearings were followed by separate trials in Docket 8918 and Docket 8917 and an Initial Decision in each of the two cases has been filed on September 1, 1978 and September 28, 1979, respectively.

The separate trial in this case began in October 1979 and the record was closed on August 26, 1980. The record testimony covers over 18,000 pages of transcript. Some forty witnesses testified, including a large number of expert witnesses, and some 410 exhibits were received in evidence. In addition, a large volume of scientific publications and material was discussed by expert witnesses. By order dated September 12, 1980, the Commission extended the date within which to file the initial decision through January 30, 1981.

Neither advertising agency is defending this action at the present time. Lois Holland Callaway, Inc. is now insolvent and its creditor's committee is not defending the action (CX 690). Dancer-Fitzgerald-

Sample, Inc. was discharged by Sterling Drug Inc. in June 1976, and has had no responsibility nor interest in respondent's products since that time. Dancer-Fitzgerald-Sample entered into a consent order agreement with complaint counsel which was signed on December 8, 1977, and made final by the Commission on July 1, 1980 (45 FR 26,344–47, April 18, 1980; 45 FR 48,606, July 21, 1980) [96 F.T.C. 1 (1980)]. [3]

Based on the Complaint, Answers and Prehearing Orders, the following issues are matters for determination in this proceeding:

1. With respect to advertising representations for Bayer:

(a) That "it was represented, directly or by implication . . ., that it has been established that . . . Bayer Aspirin is superior in terms of significant therapeutic effect to any other aspirin." (Complaint ¶ 8; *see* Contested Issues of Fact ¶ 2(a), September 25, 1973, adopted by Prehearing Order, October 3, 1973 [hereinafter "Contested Issues of Fact"])

(b) That the above representation was not established "for reasons including, but not limited to, the existence of a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of all such representations." (Complaint ¶ 9; *see* Contested Issues of Fact ¶ 3, Contested Legal Issues ¶¶ 3, 4, September 25, 1973, adopted by prehearing order, October 3, 1973 [hereinafter "Contested Legal Issues"])

(c) That "it was represented directly or by implication . . . [that] Bayer Aspirin is superior in terms of significant therapeutic effect to any other aspirin." (Complaint ¶ 10; *see* Contested Issues of Fact ¶ 4(a))

(d) That there existed "no reasonable basis" for making the above representation at the time it was made, "in that respondents lacked competent and reliable scientific evidence sufficient to support such representations." (Complaint ¶ 11; *see* Contested Issues of Fact ¶ 5; *see* Contested Legal Issues ¶¶ 1, 2)

(e) That "it was represented directly or by implication . . . that a recommended dose of Bayer Aspirin relieves nervous tension, anxiety and irritability and improves the user's mood." (Complaint ¶ 15; *see* Contested Issues of Fact ¶ 9(a))

(f) That there existed "no reasonable basis" for making the above representation at the time it was made, "in that respondents had no competent and reliable scientific evidence to support such representations." (Complaint ¶ 16; *see* Contested Issues of Fact ¶ 10; Contested Legal Issues ¶¶ 1, 2)

(g) That "it was represented, directly or indirectly, that Bayer Aspirin has been tested against [4] 220 other brands of aspirin for quality,

purity, freshness, stability, and speed of disintegration, and that the results of the tests ["223 test"] demonstrated that Bayer Aspirin is qualitatively superior to all of the other brands tested in all respects." This was interpreted by respondent as meaning overall pharmaceutical superiority. It was interpreted by complaint counsel as meaning superiority in each tested respect. On October 2, 1975, the Administrative Law Judge adopted complaint counsel's interpretation. (Complaint ¶ 20; Contested Issues of Fact ¶ 15) This position was later explained as referring to the respects enumerated in ¶ 20 of the Complaint: quality, freshness, stability, and speed of disintegration (Order Denying Complaint Counsel's Motion for Summary Judgment, October 24, 1975, note page 6; Oral Argument on Motion for Partial Summary Judgment, October 22, 1975, pp. 24–25).

(h) That the so-called "223 test" does "not demonstrate that Bayer Aspirin is qualitatively superior in all respects, including speed of disintegration, to all other aspirins tested." (Complaint ¶ 21; *see* Contested Issues of Fact ¶ 16; Contested Legal Issues ¶¶ 3, 4)

(i) That it was represented that the "223 test" "demonstrated that Bayer Aspirin is . . . therapeutically superior to all of the other brands tested." (Complaint ¶ 20; *see* Contested Issues of Fact ¶ 17)

(j) That the "223 test" does "not demonstrate that Bayer is therapeutically superior to all other brands because at the time of such representations there existed a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drug product, concerning the validity, significance or interpretation of such tests as related to such representation." (Complaint ¶ 21; *see* Contested Issues of Fact ¶ 18; Contested Legal Issues ¶¶ 3, 4)

2. With respect to advertising representations for BCA:

(a) That "it was represented, directly or by implication . . ., that it has been established that . . . Bayer Children's Aspirin is superior in terms of significant therapeutic effect to any other children's aspirin." (Complaint ¶ 8; *see* Contested Issues of Fact ¶ 2(b))

(b) That the above representation was not established "for reasons including, but not limited to, the existence of a substantial question, recognized by [5] experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs as to the validity of all such representations." (Complaint ¶ 9; *see* Contested Issues of Fact ¶ 3; Contested Legal Issues ¶¶ 3, 4)

(c) That "it was represented directly or by implication . . . [that] Bayer Children's Aspirin is superior in terms of significant therapeutic effect to any other children's aspirin." (Complaint ¶ 10; *see* Contested Issues of Fact ¶ 4(b))

(d) That there existed "no reasonable basis" for making the above representation at the time it was made, "in that respondents lacked competent and reliable scientific evidence sufficient to support such representations." (Complaint ¶ 11; *see* Contested Issues of Fact ¶ 5; Contested Legal Issues ¶¶ 1, 2)

3. With respect to advertising representations for *Vanquish:*

(a) That "it was represented directly or by implication . . . that it has been established that:

(i) A recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin;

(ii) Because Vanquish contains 'gentle buffers' it will result in less gastric discomfort than any nonprescription internal analgesic not containing buffers; and that

(iii) A recommended dose of Vanquish is more effective for the relief of pain than the largest selling 'extra strength' tablet." (Complaint ¶ 8; *see* Contested Issues of Fact ¶¶ 2(d), 2(e), 2(f))

(b) That the above representations have not been established, "for reasons including, but not limited to, the existence of a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of all such representations." (Complaint ¶ 9; *see* Contested Issues of Fact ¶ 3; Contested Legal Issues ¶¶ 3, 4)

(c) That "it was represented directly or by implication . . . that: **[6]**

(i) A recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin;

(ii) Because Vanquish contains 'gentle buffers' it will result in less gastric discomfort than any nonprescription internal analgesic not containing buffers; and that

(iii) A recommended dose of Vanquish is more effective for the relief of pain than the largest selling 'extra strength' tablet." (Complaint ¶ 12; *see* Contested Issues of Fact ¶¶ 6(b), 6(c), 6(d))

(d) That at the time of the above representations regarding Vanquish there existed "a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of such representations" (Complaint ¶ 13; *see* Contested Issues of Fact ¶ 7; Contested Legal Issues ¶¶ 4, 5)

(e) That these representations were made "without disclosing the existence of such a substantial question as to the validity of each representation. In light of the representations made, the existence of such a substantial question is a material fact, which, if known to consumers, would be likely to affect their consideration of whether or

not to purchase such products. Thus, respondents have failed to disclose material facts." (Complaint ¶ 4; *see* Contested Issues of Fact ¶ 8; Contested Legal Issues ¶¶ 4, 6, 7)

(f) That respondent "marketed and advertised Vanquish without disclosing in the advertising for this product that it contains aspirin. . . .[1] Aspirin . . . [is a] well-known commonplace [substance] widely available in a variety of non-prescription products. Moreover, the use of aspirin . . . can be injurious to health and may cause undesirable side effects. Thus, [7] respondents have failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products." (Complaint ¶ 23; *see* Contested Issues of Fact ¶¶ 20, 21; Contested Legal Issues ¶¶ 6, 8)

4. With respect to advertising representations for *Cope:*

(a) That "it was represented, directly or by implication . . . that it has been established that a recommended dose of Cope is more effective for the relief of 'nervous tension headache' pain than a recommended dose of any other non-prescription internal analgesic." (Complaint ¶ 8; *see* Contested Issues of Fact ¶ 2(c))

(b) That the above representation was not established "for reasons including, but not limited to, the existence of a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of all such representations." (Complaint ¶ 9; *see* Contested Issues of Fact ¶ 3; Contested Legal Issues ¶¶ 3, 4)

(c) That "it was represented directly or by implication . . . that a recommended dose of Cope is more effective for the relief of 'nervous tension headache' pain than a recommended dose of any other non-prescription internal analgesic." (Complaint ¶ 12; *see* Contested Issues of Fact ¶ 6(a))

(d) That at the time the above representation was made, there existed "a substantial question, recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of such drugs, as to the validity of such representations." (Complaint ¶ 13; *see* Contested Issues of Fact ¶ 7; Contested Legal Issues ¶¶ 4, 5)

(e) That these representations were made "without disclosing the existence of such a substantial question. . . . In light of the representations made, the existence of such a substantial question is a material fact, which, if known to consumers, would be likely to affect their consideration of whether or not to purchase such products. Thus,

[1] Paragraph 23 of the Complaint also alleged that failure to disclose that caffeine is an ingredient of Vanquish was a failure to disclose a material fact which, if known to certain consumers, would be likely to affect their consideration of whether or not to purchase the product. However, complaint counsel stated that they were not pursuing the caffeine disclosure issue (Prehearing Conference Order, October 22, 1979).

respondents have failed to disclose material facts." (Complaint ¶ 14; *see* Contested Issues of Fact ¶ 8; Contested Legal Issues ¶¶ 4, 6, 7)

(f) That "it was represented directly or by implication . . . that a recommended dose of Cope [8] relieves nervous tension, anxiety and irritability and will enable persons to cope with the ordinary stresses of everyday life." (Complaint ¶ 15; *see* Contested Issues of Fact ¶ 9(b))

(g) That there existed "no reasonable basis" for making the above representation at the time it was made, "in that respondents had no competent and reliable scientific evidence to support such representations." (Complaint ¶ 16; *see* Contested Issues of Fact ¶ 10; Contested Legal Issues ¶¶ 1, 2)

(h) That respondents "referred to the results of tests or studies and represented, directly or by implication, that such tests or studies prove the claim that a recommended dose of Cope is more effective for the relief of 'nervous tension headaches' than recommended doses of all other non-prescription internal analgesics." (Complaint ¶ 18; *see* Contested Issues of Fact ¶ 13)

(i) That "the tests or studies referred to do not prove the claim that a recommended dose of Cope is more effective for the relief of 'nervous tension headaches' than recommended dose of all other non-prescription internal analgesics." (Complaint ¶ 19; *see* Contested Issues of Fact ¶ 14)

(j) That it was "represented directly or by implication that Cope contained a unique formula in that it alone among non-prescription headache remedies contained both a pain reliever and an ingredient with sedative properties . . . [and that] the ingredients referred to are aspirin and methapyrilene, both of which were available for non-prescription use in Excedrin PM. Therefore, the advertisements . . . were misleading in a material respect." (Complaint ¶ 22; *see* Contested Issues of Fact ¶ 19)

(k) That respondent "marketed and advertised Cope without disclosing in the advertising for this product that it contains aspirin. . . .[2] Aspirin . . . [is a] well-known commonplace [substance] widely available in a variety of non-prescription products. Moreover, the use of aspirin . . . can be injurious to health and [9] may cause undesirable side effects. Thus, respondents have failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products." (Complaint ¶ 24; *see* Contested Issues of Fact ¶¶ 20, 21; Contested Legal Issues ¶¶ 6, 8)

5. With respect to advertising representations for *Midol:*

[2] Paragraph 24 of the Complaint also contained allegations regarding a failure to disclose the ingredient caffeine. This issue has been abandoned. *See* n. 1, *supra.*

(a) That "it was represented directly or by implication . . . that a recommended dose of Midol relieves nervous tension, stress, fatigue and depression and improves the user's mood." (Complaint ¶ 15; *see* Contested Issues of Fact ¶ 9(c))

(b) That there existed "no reasonable basis" for making the above representation at the time it was made, "in that respondents had no competent and reliable scientific evidence to support such representations." (Complaint ¶ 16; *see* Contested Issues of Fact ¶ 10; Contested Legal Issues ¶¶ 1, 2)

(c) That respondent "marketed and advertised Midol without disclosing in the advertising for this product that it contains aspirin. . . .[3] Aspirin . . . [is a] well-known commonplace [substance] widely available in a variety of non-prescription products. Moreover, the use of aspirin . . . can be injurious to health and may cause undesirable side effects. Thus, respondent has failed to disclose in advertising a material fact, which if known to certain consumers would be likely to affect their consideration of whether or not to purchase such products." (Complaint ¶ 25; *see* Contested Issues of Fact ¶¶ 20, 21; Contested Legal Issues ¶¶ 6, 8)

(d) That it was "represented directly or by implication that the analgesic ingredients in Midol are other than ordinary aspirin and that the stimulant in Midol is other than caffeine." (Complaint ¶ 26; *see* Contested Issues of Fact ¶ 22)

(e) That the "analgesic ingredient in Midol is ordinary aspirin, and the stimulant in Midol is caffeine." (Complaint ¶ 27) **[10]**

6. The Complaint further made the following allegations with regard to inconsistent representations:

(a) That "it was represented directly or by implication . . . that Bayer Aspirin is as effective for the relief of headache pain (including 'nervous tension headache' pain) as, and will cause gastric discomfort no more frequently than, any other non-prescription internal analgesic, including Cope and Vanquish." (Complaint ¶ 17; *see* Contested Issues of Fact ¶ 11(a))

(b) That "it was represented directly or by implication . . . that Vanquish is more effective for the relief of headache pain than any aspirin, including Bayer Aspirin, and will cause less gastric discomfort than any non-buffered internal analgesic, including Bayer Aspirin." (Complaint ¶ 17; *see* Contested Issues of Fact ¶ 11(c))

(c) That "it was represented directly or by implication . . . that Cope is more effective for the relief of 'nervous tension headache' pain than any other non-prescription internal analgesic, including Bayer Aspi-

[3] Paragraph 25 of the Complaint also contained allegations regarding a failure to disclose the ingredient caffeine. This issue has been abandoned. *See* n. 1, *supra.*

rin and Vanquish." (Complaint ¶ 17; *see* Contested Issues of Fact ¶ 11(b))

(d) That respondents have "made claims for a product that are inconsistent with contemporaneous claims for other products made by the same firm." (Complaint ¶ 17; *see* Contested Issues of Fact ¶¶ 11, 12)

(e) That these representations are "mutually inconsistent." (Complaint ¶ 17; *see* Contested Issues of Fact ¶ 12; Contested Legal Issues ¶¶ 9, 10)

7. The Complaint made the following general allegations:

(a) That the excerpts from advertisements for Bayer Aspirin, Bayer Children's Aspirin, Vanquish, Cope and Midol listed in paragraph 7 of the Complaint were typical of the statements and representations made in the advertising. (Complaint ¶ 7; *see* Contested Issues of Fact ¶ 1)

(b) That the advertisements referred to in paragraph 8 of the Complaint were misleading in material respects, as alleged in Complaint ¶¶ 9, 13, 14, 15, 16, [11] 19, 20, 21, 22, 24 and 27 and constituted false advertisements. (Complaint ¶ 28; *see* Contested Legal Issues ¶ 11)

(c) That the making of claims for a product that are inconsistent with contemporaneous claims for other products made by the same firm, as alleged in Complaint ¶ 17 and the making of representations as alleged in Complaint ¶¶ 11, 13, 14 and 16, constituted and now constitute unfair or deceptive acts or practices in commerce. (Complaint ¶ 29; *see* Contested Legal Issues ¶¶ 9, 10)

(d) That "[t]he use by respondents of the aforesaid deceptive statements, representations, or claims, and the dissemination of the aforesaid false advertisements has had and now has, the capacity and tendency to mislead members of the consuming public into the erroneous and mistaken belief that said statements, representations, or claims were and are true and into the purchase of substantial quantities of said drugs of respondent Sterling Drug, Inc. by reason of said erroneous and mistaken belief." (Complaint ¶ 30)

(e) That "[t]he aforesaid acts and practices of respondents, as herein alleged, including the dissemination of false advertisements, as aforesaid, were and are all to the prejudice and injury of the public and of respondents' competitors and constituted and now constitute unfair methods of competition in commerce and unfair or deceptive acts or practices in commerce, in violation of Sections 5 and 12 of the Federal Trade Commission Act." (Complaint ¶ 32)

The proposed findings and conclusions submitted by the parties and their arguments in support thereof have been given careful consideration by me and to the extent not adopted by this Initial Decision, in

the form proposed or in substance, are rejected as not supported by the evidence or as immaterial. Any motion appearing on the record not heretofore or hereby specifically ruled upon either directly or by the necessary effect of the conclusions in this Initial Decision are hereby denied.

Upon consideration of the entire record in this proceeding and having considered the demeanor of the witnesses, I make the [12] following findings of fact and conclusions of law and order based on the record considered as a whole.[4]

FINDINGS OF FACT

I. INTRODUCTION

A. *Identity of Respondents and the Nature of Their Businesses*

1. Sterling Drug Inc. is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware with its office and principal place of business located at 90 Park Avenue, New York, New York (Statement of Noncontested Issues, ¶ 1).

2. Dancer-Fitzgerald-Sample, Inc. is a corporation organized, existing and doing business under and by virtue of the laws of the State of Delaware with its office and principal place of business located at 347 Madison Avenue, New York, New York (*Id.* ¶ 2). On December 8, 1977, DFS agreed to an Order to Cease and Desist in this matter conforming to the requirements of Section 2.32 of the Commission Rules. The Decision and Order with respect to DFS was issued July 1, 1980 [96 F.T.C. 1 (1980)].

3. Lois Holland Callaway, Inc. is a corporation organized, existing under and by virtue of the laws of the State of New York with its office and principal place of business [13] located at 745 Fifth Avenue, New York, New York (Answer of LHC, ¶ 2). On or about September 1978, LHC ceased doing business because of its insolvency. Its affairs are presently managed by an informal creditors committee. On October 24, 1979, co-counsel to the creditors committee notified complaint

[4] For the purposes of this Initial Decision, the following abbreviations were used:

F. – Finding of Fact in this Decision.
CPF – Complaint Counsel's Proposed Findings.
CB – Complaint Counsel's Memorandum In Support of Proposed Findings.
CRB – Complaint Counsel's Memorandum In Support of Reply Findings.
RPF – Sterling's Proposed Findings.
RB – Sterling's Post-Trial Memorandum.
RRB – Sterling's Post-Trial Reply Memorandum.
Tr. – Transcript of hearings, sometimes preceded by the name of the witness.
CX – Complaint counsel's documentary exhibit.
RX – Sterling's documentary exhibit.
Comp. – Complaint.
Ans. – Answer.

counsel that neither stockholders nor former officers of LHC intended to present any defense in the instant proceeding (CX 680A-D).

4. Thompson-Koch is an unincorporated division of Sterling, which at all times pertinent to this action has acted *inter alia* as an in-house advertising agency for Midol (CX 678, admission 220; Hartman, Tr. 9135). Glenbrook Laboratories ("Glenbrook") is an unincorporated division of Sterling, which at all times pertinent to this proceeding has had responsibility for marketing all the products involved in this proceeding (CX 678, admission 38). The Sterling-Winthrop Research Institute ("SWRI") was at all times pertinent to this proceeding, an unincorporated research division of Sterling (CX 678, admission 39).

5. Sterling is now and has been engaged in the manufacturing, offering for sale, sale and distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Midol," "Cope," and "Vanquish" (Statement of Noncontested Issues, ¶ 4). In the course and conduct of its business, Sterling causes these products, when sold, to be transported from its places of business located in various States of the United States to purchasers located in various States of the United States and in the District of Columbia. Sterling maintains and at all times relevant to the proceeding has maintained a substantial course of trade in these products in commerce. The volume of such business has been substantial (Answer of Sterling, ¶ 5).

6. From 1969 through 1973 annual consumer sales for Bayer Aspirin, Bayer Children's Aspirin, Midol, Vanquish and Cope averaged $52.6 million, $9.38 million, $3.9 million, $4.9 million and $2.57 million, respectively (CX 575A-E). In 1969, the average retail price for 100-tablet bottles of Bayer Aspirin was $1.01; the average wholesale price for a 36-tablet package of Bayer Children's Aspirin was $.22; the average wholesale price for a 60-tablet package of Cope was $.71; and the average wholesale price for a 30-tablet package of Midol was $.59 (CX 575A-B, D-E).

7. Bayer Aspirin, Bayer Children's Aspirin, Cope, Midol and Vanquish are nonprescription analgesic products which come within the classification of drugs as the term "drug" is defined in the Federal Trade Commission Act (Answer of Sterling, ¶ 3).

8. The designation, active ingredients and directions for use of these nonprescription analgesic drugs is set forth in paragraph 3 of the Complaint, and is adopted and incorporated by reference at Statement of Non-Contested Issues, paragraph 7 and admissions 965–68 of CX 678, as follows: [14]

Bayer Aspirin (per tablet):

324 milligrams (mg) aspirin.

Dosage: 1 or 2 tablets with water every 4 hours, as necessary, up to 12 tablets a day.

Bayer Children's Aspirin (per tablet):

Aspirin 81 mg

Dosage: Varies with age of child.

Cope (per tablet):

Aspirin 421.2 mg
Caffeine 32 mg
Methapyrilene fumarate 12.5 mg

Buffers:

Aluminum hydroxide 25.0 mg
Magnesium hydroxide 50 mg

Dosage: 1 or 2 tablets every 4 hours as needed, up to 9 tablets per day.

Midol (per tablet):

Aspirin 453.6 mg
Caffeine 32.4 mg
Cinnamedrine hydrochloride 149 mg

Dosage: 2 Midol tablets with water. Repeat 1–2 tablets every 4 hours as needed, up to 9 tablets per day.

Vanquish (per tablet):

Aspirin 227 mg
Acetaminophen 994 mg
Caffeine 33 mg

Buffers:

Aluminum hydroxide 25 mg
Magnesium hydroxide 50 mg

Dosage: 2caplets with water. Can be repeated every 4 hourss if needed, up to 12 caplets per day.

9. In the course and conduct of its business, Sterling disseminated, and caused to be disseminated, certain advertise[**15**]ments concerning Bayer Aspirin, Bayer Children's Aspirin, Cope, Midol and Vanquish, by United States mail and by various means in commerce, including, but not limited to, advertisements inserted in magazines and newspapers, and by means of television and radio broadcasts transmitted by television and radio stations located in various States of the United States, and in the District of Columbia, having sufficient power to carry such broadcasts across state lines, for the purpose of inducing or which were likely to induce, directly or indirectly, the purchase of these drugs in commerce (Answer of Sterling ¶ 6). These activities have included the dissemination of the advertising representations challenged in this proceeding.

10. In promoting these products by advertising from 1969 through 1973 Sterling spent at least $86.5 million for Bayer and $15.5 million for Vanquish; for advertising from 1969 through 1972, $11.4 million for Bayer Children's Aspirin; for advertising from 1969 through 1970, $5 million for Cope and $2.1 million for Midol (CX 575A-E). Thus annual advertising expenditures from 1969 through 1973 have averaged approximately $17.3 million for Bayer and $3.1 million for Vanquish; from 1969 through 1972, $2.8 million for Bayer Children's Aspirin; and from 1969 through 1970, $2.5 million for Cope and $1 million for Midol. Average ad to sales ratio for Bayer for the 1969–1973 period amounted to 33% (17.3/52.6) (F. 6, *supra*).

11. In 1969 the average retail price per tablet was $.0044 for non-Bayer plain 5-grain aspirin, as compared with $.0101 for Bayer; the average 100-tablet bottle price was $.44 for non-Bayer aspirin, compared with $1.01 for Bayer (CX 575A, F). These figures show that in 1969 consumers were paying nearly two and a half times more for Bayer than for non-Bayer plain 5-grain aspirin.

12. Bayer Aspirin competes in the over-the-counter internal analgesic market. The prime competitors in that category are Anacin, Bufferin, Excedrin, Tylenol (nonaspirin product), and a large group of plain 5-grain aspirin brands (Alberts, Tr. 8918; Miles, Tr. 9360).

13. Bayer is the only 5-grain aspirin nationally advertised on television (Alberts, Tr. 8919; Miles, Tr. 9360). Advertising for all other 5-grain aspirins is limited to in-store promotions at the retail level, print advertising, and a very small amount of spot television (Alberts, Tr. 8919; Mattimore, Tr. 15384–85). Bayer Aspirin is the only 5-grain aspirin with 100% distribution in food and drug outlets. The other 5-grain aspirin brands have regional or limited distribution (Alberts, Tr. 8919–20; Miles, Tr. 9360).

14. Sterling regularly purchased and used Nielsen data on the analgesic market. Nielsen marketing data for the analgesic [16] market reports upon the principal brands in the market and upon a category of "All Other Adult Aspirin." This category consists of all straight aspirin brands in the market apart from Bayer: branded aspirin such as Squibb, McKesson, Norwich, St. Joseph and store brands or private-label aspirin (Alberts, Tr. 8988; Mattimore, Tr. 15383–85).

15. Bayer Aspirin's market share has declined relative to the other major analgesic brands in the last 30 years (Alberts, Tr. 8995–96). In the early 1950's, Bayer's share of the analgesic market (in dollar sales) was 25%, Anacin 20%, Bufferin 2%. In 1957, the market shares were Bayer 16%, Anacin 18%, Bufferin 15–18% (Alberts, Tr. 8995; Miles, Tr. 9362). In 1960, the market shares were Bayer 15%, Anacin 17%, Bufferin 12%, Excedrin 8–9% (Alberts, Tr. 8995–96; Miles, Tr. 9362).

16. RX 291 presents Nielsen marketing data for Anacin, Bayer, Bufferin, Excedrin, Vanquish, Cope, Tylenol and All Other Adult Aspirin for the period from 1968 through 1979, showing market shares in dollar and tablet sales (RX 291; Alberts, Tr. 8968). From 1968 to 1979, Tylenol went from virtually no share to being the market leader with more than 25% of the dollar market, which is more than twice the share of its closest competitor, Anacin (RX 291A; Alberts, Tr. 8967–68). From 1968 to 1979, there was a downtrend in market share of Bayer Aspirin in both dollars and tablets (RX 291A, C; Alberts, Tr. 8974). In 1968, Bayer had 16.5% of the market in dollar sales, 27.2% in tablet sales. In 1979, Bayer had dropped to 9.9% of the market in dollar sales, 17.8% of the market in tablet sales (RX 291B, D).

17. Tablet sales data demonstrates that Bayer Aspirin, the traditional leader among 5-grain aspirin brands, has lost its leadership to the All Other Aspirin group. In 1968, Bayer had 27.2% of the tablet market compared to 23.8% for All Other Aspirin. In 1979, Bayer had 17.8% of the tablet market compared to 20.6% for All Other Adult Aspirin. Over the decade, its decline was almost three times that of the All Other Aspirin group (RX 291D; Alberts, Tr. 8974–75).

18. The store brands and private-label brands of aspirin, which number in the hundreds, are manufactured by a relatively small number of tableting companies, about 20–25 (Alberts, Tr. 9046; Mattimore, Tr. 15352–53). These brands are purchased by stores and private-label distributors on a price basis, annually or periodically, so that purchases of the same brand can be from a number of different manufacturing sources over time (Alberts, Tr. 8954; Mattimore, Tr. 15348–49; *see* Miller, Tr. 6980).

19. The analgesic market is a heavily advertised product category (Alberts, Tr. 8959–60; Miles, Tr. 9359–60; RX 292, RX 413B). From 1967 through 1973, the national television advertisers in the analgesic product category were Anacin, [17] Bufferin, Excedrin and Bayer Aspirin. Advertising expenditures were:

	Bayer (millions)	[Combined] Anacin, Bufferin, Excedrin (millions)
1967	$15.7	$37.1
1968	16.3	39.4
1969	17.9	45.3
1970	17.8	48.5
1971	18.0	53.1
1972	18.1	49.3
1973	14.7	45.9

(RX 292)

20. The combination products have made and continue to make claims of superiority to plain aspirin—Bufferin that it is faster and gentler, Excedrin that it is stronger, Anacin that it is stronger. In the past several years, with the growth of comparative advertising, more advertising has been directed against Bayer by name, rather than against aspirin (Alberts, Tr. 8988–89; RX 413C-P; Complaint Counsel's Admission Nos. 100–129; *see* Ross, Tr. 6092–94).

21. Bayer advertising is the only national advertising that defends plain 5-grain aspirin against the anti-aspirin advertising of buffered and combination aspirin products (Alberts, Tr. 8993–94; RX 402G-H; *see* Ross, Tr. 6099–6101).

22. In the early 1950's, respondent Sterling complained to the Federal Trade Commission about advertising for Bufferin, at that time a rather recent entrant. It contended that Bufferin advertising improperly represented that it was safer than aspirin, faster-acting than aspirin and that it was other than aspirin. Documents relating to this complaint are in the record as CX 371, RX 407 and RX 156.

23. Until the early 1970's, the Federal Trade Commission failed to take any action against Bufferin. After years of correspondence and a meeting with officials of the FTC, Sterling was led to believe that, in FTC staff's view, there was no basis for challenging the Bufferin claims under the FTC Act (CX 371, RX 156, RX 407). The FTC's failure to take any action and the inroads made by Bufferin (and later Excedrin) were among the factors considered and relied upon by respondent in developing the combination products which it introduced in the 1960's, Vanquish and Cope (Alberts, Tr. 8961; Tainter, RX 284R-S; Trout, Tr. 16104; RX 407A-H). Vanquish was introduced as an "extra-strength" product in the analgesic market segment promoted and defined as such by Excedrin (Alberts, Tr. 9012). Cope was introduced as a formulation designed for nervous tension headache (Tr. 15401–05). [18]

24. Vanquish and Cope have been minor factors in the analgesic market. During the period in which Vanquish advertisements challenged in this case were disseminated, the products accounted for 1.4% to 1.6% of the analgesic market. Since 1974, Vanquish's market share has steadily declined and in 1979 accounted for 1.1% of the analgesic market (RX 291B; CX 633). Cope's market share was 1% in 1969 to .7% in 1971; thereafter, Nielsen data was not collected for Cope (RX 291).

25. Vanquish advertising terminated in 1977. According to Sterling, there are no plans now or in the future to resume Vanquish advertising (Alberts, Tr. 9013).

26. During the period in which the challenged Cope advertisements were disseminated, Cope's market share ranged from 1% (in 1969) to

0.7% (in 1971) (RX 291B). Cope advertising terminated in 1971. According to Sterling, there are no plans to resume such advertising (Alberts, Tr. 9013). Indeed, the product in the form sold in 1969–71 is no longer on the market; it has been reformulated as a result of FDA action.

27. Midol is a specialized product, designed and promoted for the relief of menstrual symptoms. It is one of two products in the menstrual remedies category of the analgesic market (Hartman, Tr. 9136, 9142).

28. LHC has been an advertising agency for Sterling and has prepared, placed for publication and disseminated advertising material for "Vanquish" for all purposes of this proceeding after April 1971 (LHC Answer, ¶¶ 4, 6).

29. Sterling is now and has been engaged in substantial competition in commerce with other firms in the sale of drug products of the general kind and nature as those sold by Sterling, and LHC has been in substantial competition in commerce with other advertising agencies (Statement of Non-Contested Issues, ¶ 13).

II. THE BACKGROUNDS AND QUALIFICATIONS OF CERTAIN WITNESSES WHO TESTIFIED IN THIS PROCEEDING

A. *For Complaint Counsel*

Timothy C. Brock, Ph.D.

30. Dr. Timothy C. Brock is a Professor of Psychology at Ohio State University and is a licensed psychologist. Dr. Brock holds a Ph.D. from Yale University in psychology with a specialization in social psychology. In 1955 he joined the Yale Communication and Attitude Change Program and began a career in [19] the field of persuasion and communication. Since that time Dr. Brock has had extensive experience in evaluating the formation, reinforcement and endurance of beliefs and attitudes. This experience includes extensive experience in conducting and evaluating research in this area, including research regarding the formation of attitudes about consumer goods and services (Brock, Tr. 5043–44, CX 605).

31. Since 1957, Dr. Brock has contributed extensively to the body of literature regarding the role of communication in attitude formation and change. His numerous publications include research and analyses of persuasion techniques, measurement of attitude change, and identification of public opinion and attitudes (CX 605). Dr. Brock's research has also included studies on the endurance of beliefs and attitudes (Brock, Tr. 5051–52). Dr. Brock has performed two studies that address the role of persuasive communications on consumer perceptions of the performance of drugs (Brock, Tr. 5054–55).

32. Dr. Brock is a member of many professional associations in the fields of psychology and consumer psychology, including the American Psychological Association, the American Sociological Association, the Society of Experimental Social Psychology and the American Association for the Advancement of Science. He is a Fellow in the American Psychological Association, the American Sociological Association and the American Association for the Advancement of Science, and has been elected Secretary-Treasurer of the Evaluation Research Society, a national society of professionals concerned with the measurement and assessment of the long-term efficacy of various social and educational programs (Brock, Tr. 5045–47). Dr. Brock has also served on the editorial boards of several professional journals and has frequently reviewed articles submitted for publication to a number of other professional journals relating to the formation and persistence of attitudes. The research includes work in the field of belief formation and change, the measurement of beliefs and attitudes, and the effectiveness of various types of communication to induce attitude change (Brock, Tr. 5049).

33. Dr. Brock is a well-qualified expert in social psychology, with special expertise in the techniques of persuasion and the source and duration of consumer beliefs and attitudes, including the design and analysis of research addressing those areas.

Thomas J. DeKornfeld, M.D.

34. Dr. Thomas J. DeKornfeld, a Professor of Anesthesiology at the University of Michigan Medical School, is a recognized authority in the field of analgesic testing (DeKornfeld, Tr. 8325). His involvement in the clinical testing of analgesics dates back to the late 1950's when he began working with [20] Dr. Louis Lasagna (DeKornfeld, Tr. 8369). Since that initial involvement, Dr. DeKornfeld has conducted between 30 and 40 clinical studies on a variety of drugs, with the majority of these studies being performed with analgesics (DeKornfeld, Tr. 8330–31). Included within these clinical studies have been tests using over-the-counter analgesics. In a major study conducted in the late 1950's, Drs. DeKornfeld and Lasagna examined the comparative efficacy of over-the-counter analgesics and placebos. The results of this study were published in the *Journal of the American Medical Association* (DeKornfeld, Tr. 8332; CX 615E). Before joining the faculty of the University of Michigan Medical School, he was the Director of Therapeutic Research for Parke, Davis and Company, a major pharmaceutical corporation, and supervised all of the clinical research activities of the firm in the United States and Canada (DeKornfeld, Tr. 8326; CX 615A).

35. For the last 14 years Dr. DeKornfeld has served as Secretary of

the University of Michigan Medical School's Committee to Review Grants for Clinical Research and Investigation Involving Human Beings. In this capacity, he, along with other committee members, reviews all research protocols for studies involving human subjects conducted under the auspices of the University's Medical School (DeKornfeld, Tr. 8334; CX 615C). Dr. DeKornfeld has also participated in the evaluation of the designs of analgesic clinical tests as a member of the Consulting Board to the U.S. Veterans Administration Cooperative Analgesic Study (DeKornfeld, Tr. 8334). Dr. DeKornfeld has also published many articles in recognized medical journals involving analgesics and analgesic testing (CX 615D-H). Dr. DeKornfeld has also served as consultant to some of his medical colleagues who have had problems with patients relating to pain and the use of analgesics. In his medical practice, Dr. DeKornfeld has used analgesic drugs in clinical situations (DeKornfeld, Tr. 8337–38). Dr. DeKornfeld is eminently qualified to give expert testimony regarding analgesics, clinical testing, and clinical analgesic testing.

Richard S. Farr, M.D.

36. Dr. Richard S. Farr is Chairman of the Department of Medicine of the National Jewish Hospital in Denver. Dr. Farr, who is widely recognized as a preeminent researcher in immunology, has had extensive clinical training in the diagnosis and management of bronchial asthma and allergy, including the asthma and allergic effects associated with aspirin. He previously headed the allergy/immunology sections at the University of Pittsburgh and the Scripps Clinic in La Jolla, California, and is also known for the development of the so-called Farr test which is still widely used in immunology research (Farr, Tr. 2541–50). [21]

37. Dr. Farr has been deeply involved in the clinical study of aspirin side effects since 1969 and is responsible for the development of the aspirin challenge procedure originating at the National Jewish Hospital. Dr. Farr has had extensive experience in the design, execution and analysis of clinical tests of the side effects of aspirin, and has published widely on the topic. His experience extends to the clinical management of asthmatic and allergic patients and he has widely lectured and taught on this topic.

38. Dr. Farr served as the president of the American Academy of Allergy and has been associated with many other professional associations with particular interest in asthma and allergy. Dr. Farr is also a Distinguished Service Professor of the University of Chicago and is the recipient of the Borden Award for his outstanding work in the area of immunology (Farr, Tr. 2541–62).

39. Based on his background and experience, Dr. Farr is eminently

qualified to speak regarding asthma and allergy in general, and particularly about the asthmatic and allergic effects of aspirin and aspirin containing drugs.

Morton I. Grossman, M.D.

40. Dr. Morton I. Grossman's qualifications as an expert in gastroenterology, specifically with respect to the side effects of aspirin and antacid drugs and buffers, have been stipulated to by counsel (Grossman, Tr. 7448).

41. Dr. Grossman is recognized as one of the preeminent researchers and practitioners of gastroenterology in the world. Dr. Grossman, who currently directs the Center for Ulcer Research and Education in Los Angeles, is a Senior Medical Investigator in the Veterans Administration Wadsworth Hospital in Los Angeles, and has been Chief of the Gastrointestinal Section at the Veterans Administration Hospital in Los Angeles. Dr. Grossman is also a professor of medicine and physiology at the University of California at Los Angeles, has taught at major medical schools throughout the country and has served as a member of or advisor to many distinguished professional groups, including the National Academy of Science, National Research Panel on Gastrointestinal Drugs, the FDA's OTC Panel on Antacids and the Gastrointestinal Drug Advisory Committee of the FDA (Grossman, Tr. 7452–53; CX 612A–C).

42. Dr. Grossman's experience includes years of clinical practice with patients suffering gastrointestinal diseases, as well as considerable research in the areas of physiology and gastroenterology. Dr. Grossman has done research on the mechanism and effects of aspirin ingestion on the gastrointestinal tract and has published many articles on this subject in learned journals. Dr. Grossman has also served on various editorial boards of scientific journals, such as the [22] *American Journal of Physiology,* and has chaired the editorial board of *Gastroenterology,* the official journal of the American Gastroenterological Association. He currently serves as a member of the editorial board of *Clinical Trials* which publishes articles dealing with problems that arise in designing and conducting clinical trials. Dr. Grossman has published over 350 articles in journals, contributed to scores of textbooks and other resource works on gastroenterology (Grossman, Tr. 7452–57; CX 612A–Z014).

43. Dr. Grossman has also been the recipient of major awards and honors in his field, including the Friedenwald medal of the American Gastroenterological Association which is its highest award. He also has held high offices with many of the professional societies concerned with problems of gastroenterology (Grossman, Tr. 7457–58; CX 612C).

44. Based on his education and training, as well as his wealth of research and clinical experience, Dr. Grossman is eminently qualified to speak to gastroenterology generally and specifically to gastrointestinal effects of aspirin and aspirin-containing products, including the effect of buffers in such products.

Robert John, M.D.

45. Dr. Robert John was Medical Director of Glenbrook Laboratories, a Division of Sterling, from June 1971 through October 1974 (John, Tr. 5486; CX 678, admission 106). He received his M.D. degree from the University of London King's College Hospital Medical School, was an intern at the Metropolitan Hospital in London, England, and recently was a resident at the New York Medical College (John, Tr. 5484–85; CX 624A). From 1960 through 1975, Dr. John worked in the pharmaceutical industry. From 1960 to 1962, Dr. John was Assistant Medical Director of Bristol-Myers' Products and International Divisions; from 1962 to 1965, he was Senior Clinical Research Associate at Warner-Lambert Research Institute, U.S.A.; from 1965 to 1967, he was Associate Medical Director of E.R. Squibb and Sons; from 1967 to 1968, he was Medical Director at Squibb Products Company; from 1968 to 1970, he was Medical Director at Squibb Beech-Nut, Inc.; and from 1970 through June 1971, he was Associate Medical Director of Winthrop Laboratories (John, Tr. 5486–87; CX 624C, D). In these positions, his responsibilities included clinical research into the safety and efficacy of drugs, including OTC analgesics, and review of advertising (John, Tr. 5487–88).

46. As Medical Director of Glenbrook Laboratories, Dr. John's responsibilities included reviewing advertisements and promotional materials with respect to medical claims, recommending clinical investigations, and keeping current with the medical literature concerning OTC analgesic agents (John, Tr. 5490, 5495). As part of his responsibility concerning the [23] review of advertising, Dr. John met with representatives of the advertising agency to insure that any medical claims appearing in proposed advertisements were substantiated (John, Tr. 5495–96). He also reviewed completed advertisements for all Glenbrook Laboratories products (John, Tr. 5504–06). According to Dr. John, he was the only Glenbrook Laboratories official to review advertisements for Bayer Aspirin, Bayer Children's Aspirin, Midol, Cope, and Vanquish from the viewpoint of medical substantiation, although he consulted occasionally with his superior, Dr. Monroe Trout, Vice President and Director of Medical Affairs for Sterling (John, Tr. 5490–92, 5495–96, 5504–05, 5578–80).

47. From time to time, Dr. John made presentations concerning the medical aspects of Glenbrook products to Sterling's Board of Directors

and other corporate executives (John, Tr. 5496–98). Dr. John also served on Glenbrook Laboratories' Executive Management Committee which reviewed Glenbrook's marketing strategy (John, Tr. 5491–94). This committee also included the President of Glenbrook, the Executive Vice President and the Group Product Managers. Similarly, Dr. John served on the corporate Aspirin Committee which reviewed developments in aspirin research (John, Tr. 5490–92, 5495).

48. Dr. John was chosen to represent Sterling before government and industry committees. He represented Sterling before the FDA's OTC Internal Analgesic Panel on the matter of aspirin warnings. He was also chosen to represent Sterling on the Proprietary Association Task Force on Special Analgesic Products (John, Tr. 5498–5503). By virtue of his personal involvement and opportunity to observe salient events at Sterling during the time when many of the challenged advertising claims were allegedly made, Dr. John is in a unique position to give evidence on the nature and quality of Sterling's advertising substantiation, with respect to aspirin products.

Orville H. Miller, Ph.D.

49. Dr. Orville H. Miller is a Professor of Pharmacy at the University of Southern California, School of Pharmacy, in Los Angeles, California. For over thirty years he has taught in the areas of pharmacy practice, industrial pharmacy, quality control and product development, which include the study of product formulation and pharmaceutical analysis (Miller, Tr. 6674). Dr. Miller has been chosen as a Fulbright Professor and taught at the University of Cairo for one year (Miller, Tr. 6677).

50. Dr. Miller has extensive experience in the area of pharmaceutical chemistry. He has served as a pharmaceutical consultant to numerous laboratories, hospitals, and committees since 1952, consulting in the areas of pharmaceutical quality, disintegration, bioavailability, pharmaceutical analysis and product formulation. Dr. Miller worked as a consultant to [24] Robinson Laboratories for eight years. His work there in part involved insuring compliance with the FDA's Good Manufacturing Practice Regulations. Specifically, he performed disintegration tests on a large variety of aspirin and aspirin-containing products. He has done similar consulting work concerning aspirin with other laboratories. In his consulting work, Dr. Miller has examined well over one hundred samples of aspirin and aspirin-containing products for pharmaceutical elegance, disintegration, dissolution, stability and bioavailability (Miller, Tr. 6686–99; CX 623A, B).

51. Dr. Miller was elected and served for ten years, from 1960–1970, as a member of the United States Pharmacopoeia Revision Committee, which establishes standards to insure the pharmaceutical quality

of drug products. These standards are officially recognized by the Food and Drug Administration. Dr. Miller reviewed or developed over thirty-six monographs which establish standards for the analytical procedures and purity tests for drugs. He has also served for three years on the Committee on Physiological Availability of Drugs, a joint committee of the United States Pharmacopoeia and the National Formulary, which was concerned with developing testing procedures to insure dissolution of drug products (Miller, Tr. 6677–84).

52. Dr. Miller has been a member of a number of professional societies in the fields of pharmacology, and has held several offices, including president of the American College of Pharmacists and chairman of the Practical Pharmacy Section of the American Pharmaceutical Association (Miller, Tr. 6684–85). He has served on a number of committees for professional societies, such as the Formulary Task Force of the California Pharmaceutical Association and a committee of the Academy of Pharmaceutical Science, which investigated potential problems concerning the bioavailability of drugs (Miller, Tr. 6685).

53. Based on his background, training, and experience, Dr. Miller is an expert well qualified to speak to the pharmaceutical quality of aspirin, specifically in the areas of pharmaceutical chemistry, pharmaceutical analysis, dissolution and bioavailability.

Charles G. Moertel, M.D.

54. Dr. Charles G. Moertel, who presently serves as the Director of the Mayo Clinic's Comprehensive Cancer Center, Chairman of its Department of Oncology, and Professor of Medicine at the Mayo Medical School, is an expert in evaluating analgesic studies using subjective pain response methodology and is preeminent in the field of clinical testing of drugs. Dr. Moertel's expertise in the analysis of patients' subjective responses to various kinds of drugs, including analgesics, has been developed over the last 24 years through his clinical and research activities at the May Clinic (Moertel, Tr. 6234–36; CX 621A). [25]

55. At the Mayo Clinic, Dr. Moertel is involved in the evaluation of therapeutic agents. His involvement covers all of the Clinic's treatment programs designed to deal with malignant diseases starting in the gastrointestinal tract. He has done a great deal of work over an extended period of time in the evaluation of symptomatic and supportive care of cancer patients, and this involvement has encompassed the evaluation of analgesic agents, antiemetic agents, and diuretic agents (Moertel, Tr. 6240–42).

56. Dr. Moertel's work with analgesics evolved from the primary need of his advanced cancer patients to have effective treatment for

pain. Since the predominant part of his practice was to treat patients whose conditions had advanced beyond a point where surgery could help, but who suffered from mild to severe pain, Dr. Moertel developed an interest in the comparative efficacies of the available analgesics. He conducted two studies involving numerous OTC and prescription oral analgesics to determine their comparative efficacies in relieving pain. These studies were published in leading medical journals subject to peer review (Moertel, Tr. 6240–44; CX 621J, Q).

57. Dr. Moertel has also evaluated some of the newer chemical agents developed by pharmaceutical companies for analgesics purposes. He has conducted a number of clinical studies using antiemetic and chemotherapeutic drugs as well (Moertel, Tr. 6242). In all of these studies, Dr. Moertel has been involved in the analysis and evaluation of patients' subjective responses (Moertel, Tr. 6243).

58. In addition, Dr. Moertel has authored articles dealing with analgesics in a broader sense and drawing upon his clinical experience in the management of cancer pain. These articles have appeared in several textbooks of which he has been the primary author, or in which he was invited by the primary author to contribute (CX 680E, F, G, J, K; CX 621G, H, I, K, L).

59. As a practicing physician, Dr. Moertel prescribes, administers, and advises patients on a daily basis in the use of analgesics, including aspirin (Moertel, Tr. 6243–44).

60. Dr. Moertel is a member of the FDA's Oncologic Drugs Advisory Committee and advises the FDA on clinical test protocols for new drugs intended for use in the treatment of cancer patients. Dr. Moertel also serves on the Phase One Study Group of the National Cancer Institute and helps to evaluate the types of protocols that will be most appropriate to determine the clinical value of new agents for the treatment of malignant diseases (Moertel, Tr. 6238). Dr. Moertel is eminently qualified to present expert testimony concerning clinical tests, the evaluation of patients' subjective responses, and the clinical testing of analgesics. **[26]**

Donald D. Stevenson, M.D.

61. Dr. Donald D. Stevenson is a member of the allergy/immunology division at the Scripps Clinic in La Jolla, California. Dr. Stevenson, who also holds a clinical appointment in the Department of Internal Medicine at the University of California, has extensive experience in the diagnosis and management of patients suffering from various allergies and asthmatic conditions, including those associated with aspirin. He has designed and conducted clinical tests of drugs to determine their safety and effectiveness in treating asthmatic and allergic conditions and has conducted clinical tests and controlled challenges

in order to determine the asthmatic and allergic effects of aspirin ingestion.

62. Dr. Stevenson has lectured and taught generally on the subject of immunology and particularly on the asthmatic and allergic effects of aspirin ingestion. He has published articles and studies relating to these topics and is familiar with the literature and current thoughts regarding aspirin side effects.

63. Dr. Stevenson is associated with various scientific and medical groups, including the American Academy of Allergy and the West Coast Allergy Society, with primary interest in asthma and allergy and has participated in meetings and conferences held by such organizations (Stevenson, Tr. 1454–71). Based on his background, training and experience, Dr. Stevenson is highly qualified to speak to immunology, asthma and allergy generally and specifically to the asthmatic and allergic side effects of aspirin and aspirin-containing products.

Karl Rickels, M.D.

64. Dr. Karl Rickels, Professor of Psychiatry and Pharmacology at the University of Pennsylvania, is an eminent practitioner with extensive training and experience in the diagnosis and management of patients exhibiting nonpsychotic symptoms such as anxiety and tension. He directs the Private Practice Research Group, funded by NIH, which is the only unit in the country conducting a large scale research with private patients of family physicians who suffer tension and stress (Rickels, Tr. 7895–7901, 7919–24).

65. Dr. Rickels has been Director of the Psychopharmacology Research Unit of the University of Pennsylvania since 1962, and has been appointed to an endowed chair in Human Behavior. He has also widely lectured and consulted both with industry and academics in the area of psychopharmacology and currently sits with the Clinical Pharmacology Study Session of the National Institute of Mental Health. Dr. Rickels has had extensive experience in the design, execution and review of clinical tests of drugs, including aspirin, for tension relief and has often [27] consulted with industry on the development of protocols for such clinical tests (Rickels, Tr. 7897–7902, 7906–13).

66. For three years, Dr. Rickels chaired FDA's OTC panel on Nighttime Sleep-Aids, Daytime Sedative and Stimulants, and he has published widely on psychopharmacology topics including the effects of aspirin on tension relief (Rickels, Tr. 7903, 7913–15).

67. Based on his background, training, and experience, Dr. Rickels is an eminent expert well qualified to speak to psychopharmacology and tension and particularly to the effects of aspirin and caffeine on tension.

Ivan Ross, Ph.D.

68. Dr. Ivan Ross is a Professor of Marketing at the University of Minnesota, College of Business Administration, and is a licensed consulting psychologist. Dr. Ross has had extensive training and experience in the fields of consumer psychology and behavior, and marketing and marketing research (CX 603; Ross, Tr. 5713–21). Dr. Ross is also familiar with the literature in these areas. In addition, Dr. Ross has had extensive experience working with advertisers and advertising agencies on advertising content and strategy for a wide variety of consumer goods and services and has used various consumer research techniques, such as focus groups, copy tests, penetration studies, and image studies (Ross, Tr. 5717–18, 5722–23). Dr. Ross has also been a consultant with the Food and Drug Administration's Bureau of Foods (Ross, Tr. 5724–25).

69. Dr. Ross is a member of a number of professional associations in the areas of psychology, marketing, advertising, and consumer research and he has held both elected and appointed positions within these organizations (Ross, Tr. 5725–27). He has also served as an editor and reviewer of articles and papers in consumer behavior and advertising research for journal publication presentations before various professional organizations and has presented papers before professional organizations in the areas of marketing, consumer research, and psychology. His articles, studies, and other writings in fields such as consumer beliefs, consumer behavior, and advertising have been published in peer-reviewed journals and other publications (Ross, Tr. 5727–29; CX 603). Furthermore, Dr. Ross has been chosen to arbitrate complaints about advertising for the Minnesota Advertising Review Board and to mediate consumer complaints for the Better Business Bureau of Minnesota (Ross, Tr. 5726–27). Finally, he has appeared as an expert witness in a number of legal proceedings and testified regarding the conduct and evaluation of consumer research (Ross, Tr. 5723).

70. Dr. Ross' training, professional experience, and familiarity with the literature qualify him as an expert in psychology, specializing in consumer psychology and consumer behavior, marketing, and marketing research. He gave expert [28] testimony regarding various marketing and advertising issues in this proceeding, including the meaning of advertisements and the messages advertising is likely to convey to consumers, the consumer images of Bayer Aspirin and the source and duration of such images.

B. *For Sterling Drug Inc.*

1. Respondent's Advertising Experts

Arnold E. Amstutz, Ph.D.

71. Dr. Arnold E. Amstutz is qualified as an expert in consumer marketing research, specifically as an expert in the design and evaluation of instruments to measure consumer perceptions of products and to measure the impact of communications and product experience in changing consumer attitudes and behavior (Amstutz, Tr. 9993–94).

72. Since 1959, Dr. Amstutz has been involved in the design, execution and analysis of surveys measuring the impact of communications upon consumer attitudes, behavior and perceptions of products. He has developed and used modeling and simulation techniques to study and predict market behavior, which includes behavior anticipated from advertising campaigns. This has involved the extensive use and analysis of various survey methodologies to determine the consumer perception of products, the consumer image and value system, and to evaluate the impact of advertising campaigns, usually by testing several applications of advertising strategies. Dr. Armstutz has used this approach in work on marketing and communications analysis for leading firms in the United States and Europe (Amstutz, Tr. 9984–90).

72A. Dr. Amstutz received a Ph.D. from the Massachusetts Institute of Technology (MIT). He was on the faculty at the MIT Sloan School of Management from 1967 to 1972, where he taught and conducted research on marketing strategy and the application of information technology to marketing. Since then, Dr. Amstutz has worked in connection with various organizations, including being the founder and chairman of Decision Technology, Inc., a firm engaged in designing and implementing management systems; a partner in Cantor, Achenbaum & Heekin, a market counseling firm; a founder and chairman of ISIS Systems, Inc., which is engaged in providing management information systems, including application of information technology and systems to consumer marketing communications. He has published widely in the fields of his expertise. It was in connection with ISIS Systems, Inc. that Dr. Amstutz performed the work relevant to his testimony (Amstutz, Tr. 9989–93; RX 253).

73. At the request of respondent's counsel, and under the supervision of Dr. Amstutz, ISIS Systems analyzed and reviewed two studies performed by Dr. Hans Zeisel under contract for the FTC complaint counsel (CX 520 and CX 521) and prepared documentary material which was introduced in evidence (Amstutz, Tr. [29] 9994–95). The ISIS documents—RX 141A, "Analysis of the Use of Combined

Data From TV Ad and Print Ad Surveys in the Zeisel Advertising Study, CX–520"; RX 141B, "Response Count Analyses of Survey Data Used in the Zeisel Advertising Survey, CX–520"; RX 142, "Analyses of Survey Data Used in the Zeisel Image Study, CX–521"—were prepared under Dr. Amstutz's direction and supervision (Amstutz, Tr. 9995). In addition, for rebuttal purposes, Dr. Amstutz analyzed material referred to in the testimony of Dr. Ross and Dr. Brock (*See, e.g.,* Amstutz, Tr. 10142–53, 10154–60). In this, Mr. Cortesi was responsible for preparation of the data base and review of survey design and administration, while Dr. Amstutz was responsible for overall supervision of programming criteria and for analysis of both the design and conclusions of the Zeisel studies (CX 520 and CX 521) and of the ISIS data reported in RX 141A, RX 141B, and RX 142 (Cortesi, Tr. 9784; Amstutz, Tr. 9994–95).

Robert W. Chestnut, Ph.D.

74. Dr. Robert W. Chestnut is qualified as an expert in the area of consumer psychology, particularly with regard to marketing and advertising effects, memory effects, persuasion, consumer attitudes, and consumer decisionmaking behavior (Chestnut, Tr. 12242). Dr. Chestnut is well qualified to provide expert testimony in the areas of marketing and advertising effects, memory effects, persuasion, consumer attitudes, and consumer decisionmaking. He received his Master's and Doctoral degrees in the field of consumer psychology from Purdue University. Dr. Chestnut's graduate work at Purdue began with a grant from the National Science Foundation under Professor Jacoby and involved numerous studies in the area of nondurable purchasing behavior including package label use and other aspects of consumer information search in purchasing. Analgesics was one of the product categories he studied. Dr. Chestnut's Doctoral dissertation concerned the impact which the attractiveness of an information source can have on a consumer's purchase behavior. His Master's thesis was a study of information acquisition as it is affected in shopping behavior. Since he began teaching at Columbia University, Dr. Chestnut has done considerably more work and has published extensively in the areas of persuasion and consumer information processing. He teaches graduate level courses and seminars in advertising, consumer behavior and marketing strategy, information processing in consumer decisionmaking, and persuasion in television advertising (Chestnut, Tr. 12233–41; RX 281).

75. Dr. Chestnut is a long-standing member of the Division of Consumer Psychology of the American Psychological Association and heads a committee of that organization. He is also a member of the

American Marketing Association and the Association for Consumer Research (Chestnut, Tr. 12240; RX 281).

76. In addition to his teaching and scholarly activities, Dr. Chestnut has engaged in consulting work for various organizations and companies. In the advertising area, this has involved [30] an assessment of the impact of advertisements on consumer response and a review of marketing research such as copy testing to determine how it might be used to estimate overall advertising campaign effectiveness. He has also worked in a consulting capacity with the Federal Trade Commission and the Food and Drug Administration (Chestnut, Tr. 12240–41; RX 281).

Alexander C. Cortesi

77. Alexander C. Cortesi was qualified as an expert in the methodology issues of consumer and marketing research, specifically relating to sample design, questionnaire design, coding, survey administration and data processing (Cortesi, Tr. 9783). Mr. Cortesi has had extensive experience in designing and reviewing consumer surveys and survey questionnaires. He has been involved in consumer and marketing research as well as developing information system since 1965. His work has included projects for major firms which market consumer products in the United States and Europe. From 1965 to 1971, he held senior positions in Decision Technology International, and Decision Technology America, firms engaged in marketing consulting, which included the design and use of consumer-based models to predict consumer behavior. From 1972 to 1976, he was President of Home Testing Institute, a subsidiary of American Can Company, which is engaged in contract market research, including consumer attitude and perception studies, product studies and tracking studies on a longitudinal basis. He also has had experience with sampling techniques, including national probability sampling. Since 1976, he has been President and Director of ISIS Systems, Inc., a company engaged in marketing research and information systems (Cortesi, Tr. 9766–73, 9775–83; RX 254).

Russell Haley, Ph.D.

78. Dr. Russell Haley is qualified as an expert in the design and analysis of consumer and marketing research (Haley, Tr. 10556–57).

79. Dr. Haley is a professor at the University of New Hampshire where he teaches advertising, marketing research, and marketing management at both the graduate and undergraduate levels. Prior to joining the faculty at New Hampshire in 1975, Dr. Haley taught part-time at Rutgers University and the University of Connecticut (RX 255; Haley, Tr. 10551). Dr. Haley received a B.A. degree from

Wooster College, an M.B.A. in statistics from Columbia University, and a Ph.D. in consumer behavior from Union Graduate School. Dr. Haley's dissertation was on selective perceptions (Haley, Tr. 10551–52; RX 255).

80. Dr. Haley has had extensive experience in the design and analysis of consumer and marketing research in his work at advertising agencies, market research firms, and currently, with a consulting company. Throughout his career he has been [31] involved in various kinds of consumer and marketing research including copy testing, segmentation studies, and image studies (Haley, Tr. 10553–54). Dr. Haley's professional experience in the analgesic market includes numerous copy tests and one large segmentation study which covered a complete range of consumer attitudes toward analgesics, behavior patterns, volume of use, occasions of use, classification data, and psychographic characteristics. In his advertising work, however, he has never had any responsibility for analgesic advertisements (Haley, Tr. 10557–58).

81. Dr. Haley has edited one book, written many articles, and given many speeches, all in the areas of advertising research, segmentation analysis, and attitude measurement. He belongs to a number of professional associations and has held positions in them, including editorial positions (Haley, Tr. 10555–56).

Miriam Lieber

82. Miriam Lieber is an expert in the design and execution of attitude research studies (Lieber, Tr. 16779–85; RX 426). She has a Bachelor's degree and a Master's degree from the University of Chicago, and was a Fellow at Harvard University in a Ph.D. program in educational sociology (Lieber, Tr. 16781; RX 426).

83. Miriam Lieber is President of Lieber Attitude Research, Inc., and is Chief Research Consultant to the firm's clients. As President, she also serves in a supervisory capacity in the firm. The firm's clients include Citibank, Bristol-Myers, Clairol, Hanes Corp., Procter & Gamble, many advertising agencies, and scholastic magazines. Lieber Attitude Research, Inc. performs all types of attitude research, including basic attitude research, focus group research, image tests and copy tests. Miriam Lieber has been involved with attitude research since 1951, and has been an independent consultant since 1961 (Lieber, Tr. 16779–85; RX 426).

84. Prior to becoming an independent consultant, Miriam Lieber worked for the Bureau of Applied Research at Columbia University, the National Opinion Research Center, and International Research Associates on a free lance basis from 1951 to 1953. She also edited a project done by the Bureau of Applied Social Research for the Army,

and did research for Radio Free Europe, Voice of America and International Research Associates. Miriam Lieber has also worked for Research Services, Ltd., an independent subsidiary of the British advertising agency known as the London Press Exchange, where she worked for Mark Abrams, a well-known economist and researcher. She also has worked for the Creative Research Department at Tatham-Laird, a Chicago advertising agency, where she served as [32] Associate Director (Lieber, Tr. 16781–83; RX 426). In addition to her position as an independent consultant and President of Miriam Lieber Attitude Research, Inc., Miriam Lieber sits on the New York Community Planning Board, an appointed position in New York City, and is a member of the New York Alliance for the Public Schools (Lieber, Tr. 16784; RX 426).

85. Miriam Lieber has performed hundreds of focus group studies, and much of the attitude research undertaken by her company has concerned advertising. She has done attitude research for OTC products, including Mylanta, Phillips Milk of Magnesia, Contac, and Nyquil. She has also done attitude research on all aspects of the feminine hygiene category. In addition to the study on Midol and Pamprin performed for Sterling Drug, Inc. (RX 230), Miriam Lieber has done a basic attitude research study on the menstrual protection category. She has undertaken between six and fifteen studies for Sterling (Lieber, Tr. 16784–85; RX 426).

Benjamin Lipstein, Ph.D.

86. Dr. Benjamin Lipstein is an expert in marketing research, including advertising research, the design of survey instruments and survey methodology, and in the analysis and evaluation of survey results (Lipstein, Tr. 11957). Dr. Lipstein received his Ph.D. from Columbia University in Economics and Statistics (RX 283; Lipstein, Tr. 11951).

87. Dr. Lipstein was appointed a tenured Professor of Marketing at the Graduate School of Business Administration at New York University in 1978, where he teaches graduate courses in market research, advertising research, multivariate methods in marketing, and mathematical models in marketing financial services (RX 283; Lipstein, Tr. 11945–46).

88. Prior to 1978, Dr. Lipstein was a Senior Vice-President of SSC&B, a large advertising agency, where he was responsible for all types of research activities, including advertising research, copy research, attitude research, product testing, mathematical modeling, and numerous other techniques designed to help advertisers understand advertising (Lipstein, Tr. 11946–48). In the course of his career, Dr. Lipstein has also worked at other advertising agencies and re-

search companies, and spent approximately ten years with the Bureau of Labor Statistics at the U.S. Department of Labor (Lipstein, Tr. 11949–50). Dr. Lipstein has written and lectured extensively (RX 283; Lipstein, Tr. 11950–51).

89. Dr. Lipstein has been a member of numerous professional associations, some of which are only by invitation, and has held offices in these associations. He is presently chairman of the Television Copy Research Council of the Advertising Research Foundation, a trade group (Lipstein, Tr. 11952). [33]

Virginia Miles, Ph.D.

90. Dr. Virginia Miles is an expert in advertising and marketing, with particular reference to the evaluation of representations made by advertisements, analysis of consumer beliefs, formation and duration of product images, and the analysis and evaluation of consumer and marketing research (Miles, Tr. 9253). Dr. Miles was educated at Wellesley College and Columbia University from which she received M.A. and Ph.D. degrees in psychology in 1938 and 1940, respectively (RX 252; Miles, Tr. 9241).

91. Dr. Miles has had extensive experience in the advertising profession, commencing in 1940 and continuing up to the present time. She has been involved in the design and analysis of all kinds of consumer and marketing research throughout her career. From 1940 to 1942, Dr. Miles worked at J. Stirling Getchell Advertising Agency as assistant to Dr. Ernest Dichter, founder of motivation research technique. In 1942, Dr. Miles went to work for R.H. Macy and Co. as project director in the advertising research department. When she left in 1946, Dr. Miles was Associate Director of Research and Director of Advertising Research. From 1946 to 1948, Dr. Miles taught psychology, statistics and market research courses at both the graduate and undergraduate levels at the College of the City of New York. From 1948 to 1950, she worked for Alexander Smith, a carpet and rug manufacturing company, as Director of Advertising Research (Miles, Tr. 9242–43).

92. In 1950, Dr. Miles went to work for McCann-Erickson Advertising Agency and its parent company, Interpublic. She served as Director of Motivation Research until 1955 when she was appointed Vice President and Director of Research at Marplan, a market research company set up by Interpublic. During her last two years there, she was Vice President and Director of Marketing and Research at Marschalk, an advertising agency bought by Interpublic (Miles, Tr. 9243–44).

93. Dr. Miles worked for Young & Rubicam, an advertising agency, from 1960 until 1975. She started as liaison between the creative

department and the research department. In 1961, she became Vice President of Special Planning. In 1964, she was appointed to the Strategy Review Board and the Creative Review Board. Throughout her career at Young & Rubicam, Dr. Miles worked as an in-house consultant. From 1969 until 1975, she directed CONCEPTS, Young & Rubicam's new product development and planning group (Miles, Tr. 9245–46). After 35 years in the advertising profession, Dr. Miles left her position as Senior Vice President of Young & Rubicam to become an independent consultant (Miles, Tr. 9237, 9246).

94. Dr. Miles has given speeches before such groups as the American Association of Advertising Agencies, the Association of [34] National Advertisers, the International Advertising Research Foundation (Miles, Tr. 9247). Dr. Miles has been a member of the American Association for Public Opinion Research, Advertising Women of New York, the American Association of Advertising Agencies, the Advertising Research Foundation, the American Marketing Association, and the American Psychological Association. She was one of the founders of the Society for the Psychological Study of Social Issues in 1939 (Miles, Tr. 9247–48).

2. Respondent's Scientific Experts

Gilbert S. Banker, Ph.D.

95. Dr. Gilbert S. Banker is Professor of Industrial Pharmacy and head of the Industrial and Physical Pharmacy Department at Purdue University. He is an expert in pharmaceutical technology, including principles of design, formulation, manufacture and evaluation of pharmaceutical products, particularly tablets, including aspirin tablets. He received a B.S. degree in Pharmacy from the Albany College of Pharmacy, Union University, and Master's Degree at Purdue University with a major in Industrial Pharmacy and minors in Statistics and Pharmaceutical Chemistry. Dr. Baker received his Ph.D. from Purdue University in 1957 with a major in Industrial Pharmacy and Pharmaceutical Chemistry and minors in Physical Chemistry, Statistics, Industrial Engineering and Education. In 1967, he was named head of a newly created Department of Pharmaceutics. Dr. Banker has been a consultant for many of the major drug companies in the United States, and has direct experience with industrial pharmaceutical operations. A significant part of his research and consulting work has involved aspirin. He has had a long standing relationship with Miles Laboratories of Elkart, Indiana, the manufacturer of Alka-Seltzer (Banker, Tr. 12518–21, 12543; RX 257).

96. Dr. Banker is a member of numerous scientific and professional societies, including the American Pharmaceutical Association, the

Academy of Pharmaceutical Sciences, American Chemical Society, and the American Association for the Advancement of Science. He is also a member of several honorary societies. He has received the Award for Advancement of Industrial Pharmacy granted by the Academy of Pharmaceutical Science, a prestigious body of pharmaceutical scientists in the United States. Dr. Banker was elected a Fellow of the Academy of Pharmaceutical Science in 1971. Dr. Banker's research focuses on drug product quality, improved dosage form design, and the application of optimization methods to pharmaceutical products. Dr. Banker holds several patents on drug technology he has developed (Banker, Tr. 12523–27; RX 257).

97. Dr. Banker services on the Editorial Advisory Boards of several international journals, including the *Asian Journal of* [35] *Pharmaceutical Science* and the *International Journal of Pharmaceutical Technology and Product Manufacture.* He is a member of the Editorial Advisory Board of *Drug Development and Industrial Pharmacy.* He has served in numerous leadership roles in the Academy of Pharmaceutical Science, including service on numerous committees dealing with drug product quality. He was a member of the committee that developed the APHA DRUG Product Quality Statement. He is presently Chairman of the Science and Technology Policy Committee, a post he has held since 1970. In addition, he currently serves on an APHA task force which is working on the development of standards for excipients (Banker, Tr. 12527–29; RX 257).

98. Dr. Banker has just completed a five-year term on the USP Revision Committee. He has been re-elected to serve on the USP Revision Committee for *USP XXI.* Dr. Banker has published nearly 100 articles, and recently co-edited a major new pharmaceutical text entitled *Modern Pharmaceutics.* He is currently co-editing a book entitled *Pharmaceuticals and Clinical Pharmacy Practice* with Dr. Chalmer, a clinical pharmacist at Purdue University. Many of Dr. Banker's publications deal with the tablet dosage form. His articles involve, among other things, use of lubricants in tablets, the development of new physical test methods, granulating agents for compressed tablets, the effect of water vapor transmission on the stability of aspirin tablets, dissolution testing, controlled release delivery systems, stability of aspirin, salicylic acid sublimation and its relationship to aspirin stability, the optimization of drug products, and factors affecting aspirin stability in tablets. All of these articles have been published in refereed journals subject to peer review (Banker, Tr. 12530–40).

99. As a member of the USP Revision Committee, Dr. Banker had responsibility for all of the aspirin monographs for *USP XX.* These were assigned to him based upon his extensive background working

with aspirin. As a member of the USP Revision Committee on Medicinal Chemistry, Dr. Banker was assigned as a principal reviewer and drafter of recommendations or revisions with respect to all aspirin products (Banker, Tr. 12545–49). Dr. Banker is an expert with a national and international reputation in the area of improving dosage forms of drug products (Rhodes, Tr. 11050).

Ivan D. Danhof, Ph.D.

100. Dr. Danhof is an expert in physiology with a subspecialty in gastroenterology. He has both M.D. and Ph.D. degrees. He is a Professor of Physiology at the University of Texas Health Science Center-Southwestern Medical School and Associate Professor of Physiology at the Institute of Technology, Southern Methodist University. His professional [**36**] duties involve teaching courses relating to the gastrointestinal tract (Danhof, Tr. 16845–46).

101. Although he is not a board-certified gastroenterologist and his principal interest is in research in the gastrointestinal area, Dr. Danhof sees patients in consultation. He is a staff member of the Department of Internal Medicine, Division of Gastroenterology at Methodist Hospital in Dallas, a consulting member of the Internal Medicine Department, Gastroenterology, at Grand Prairie Community Hospital and a consulting staff member in internal medicine and gastroenterology at St. Paul Hospital, Dallas (Danhof, Tr. 16847–48).

102. Dr. Danhof is a member of numerous professional societies, including the American Physiological Society, the American Institute of Nutrition, Society for Experimental Biology and Medicine, and the AAAS. He has served as a consultant to the FDA as a member of several ad hoc committees, including the FDA's Gastrointestinal Drug Advisory Committee and the FDA's advisory review Panel on OTC Drugs—Laxatives, Antidiarrheals, Emetics and Antiemetics (Danhof, Tr. 16849–57).

103. Dr. Danhof has conducted research relating to the gastrointestinal tract, involving comparative absorption studies of drugs including aspirin (Danhof, Tr. 16849–51). He has published some 70 articles, including reports of his research in the area of drug absorption, including a 1972 article on salicylates. Dr. Danhof's research of absorption, bioavailability, intestinal irritation and blood loss involving salicylates has been supported by a long-term research grant-in-aid from Sterling's Glenbrook Laboratories division, beginning in 1967 and continuing until 1976. The bulk of his work on bioavailability studies done during this period remain unpublished. Dr. Danhof has continued his consulting work with Sterling on bioavailability issues (Danhof, Tr. 16853–74). Dr. Danhof is well qualified in the field of

physiology and gastroenterology and has had a long-term involvement in absorption studies of drugs including aspirin.

Constantine F. Falliers, M.D.

104. Dr. Constantine Falliers is an expert in the field of allergy, including causes and treatment of respiratory allergy. Dr. Falliers is also a clinical pharmacologist in the treatment of respiratory allergy. By education, training and experience, Dr. Falliers is a well qualified expert (Falliers, Tr. 13236–56, 13263; RX 278).

105. Dr. Falliers is board-certified in the specialty of allergy. He received his medical degree from the University of Athens Medical School in Greece. He completed residencies at the University of Colorado Medical Center, Denver, Colorado; the California Babies and Children's Hospital, Los Angeles, [37] California; and the Kaiser Foundation Hospital, Oakland, California. He is a recipient of a Fulbright Fellowship in Basic Medical Sciences and Clinical Pediatrics, University of Colorado Medical Center (Falliers, Tr. 13236, 13242; RX 278A).

106. Dr. Falliers spends about 75 percent of his time in private medical practice in Denver, Colorado, where he treats approximately 2,000 patients per year who are suffering from various allergies. Approximately half of his patients suffer from asthma (Falliers, Tr. 13240, 13244–45). Dr. Falliers spends approximately 25 percent of his time teaching and writing in the allergy area. He has taught in the field of allergy at the University of Colorado Medical Center since 1961, and currently holds the position of Associate Clinical Professor. His teaching duties involve not only lecturing, but treating patients at the National Jewish Hospital, including the Children's Asthma Research Institute of that institution. Dr. Falliers is Attending Allergist at various hospitals, including National Jewish Hospital, St. Joseph's Hospital, and General Rose Memorial Hospital. He is also connected with the Veterans Administration Hospital in Denver, where he is responsible for the allergy clinic (Falliers, Tr. 13239–41; RX 278A).

107. Dr. Falliers has been connected with the Jewish National Home for Asthmatic Children and Children Asthma Research Institute and Hospital ("CARIH") for more than 20 years. In 1957 he undertook a fellowship in pediatric allergy and clinical research at CARIH; in 1959–63 he was Director of Clinical Services at CARIH; in 1963 through 1969 he was Medical Director; and in 1969 through 1972 he was Head of the Clinical Research Division.

108. Dr. Falliers has published more than 100 scientific articles involving such areas as factors causing allergy, measuring allergic reaction, and treatment of various allergies (Falliers, Tr. 13249–51;

RX 278C–I), including an article regarding the incidence of aspirin sensitivity in asthmatics (Falliers, Tr. 13238–52; RX 278).

109. Dr. Falliers is a member of various professional societies, including the American Academy of Allergy where he is a Fellow and on the Board of Regents, the American College of Allergists where he is a Fellow, and the Society for the Care of Asthma. He has been a consultant to the Food and Drug Administration's Over-the-Counter Cough, Cold and Allergy Remedy Panel. He is a member of the Editorial Board of the *Annals of Allergy,* a recognized journal in its field (Falliers, Tr. 13243, 13248, 13254; RX 278B).

Alvan R. Feinstein, M.D.

110. Dr. Alvan R. Feinstein is a recognized expert in the history, design and use of randomized controlled trials as a [38] method for evaluating the clinical effectiveness of drugs (Feinstein, Tr. 16208, 16217; RX 279). Dr. Feinstein's reputation in the field of clinical testing is known to complaint counsel's witness (DeKornfeld, Tr. 8521).

111. Dr. Feinstein is Professor of Medicine and Epidemiology at Yale and Director of the Robert Wood Johnson Clinical Scholars Program. He earned a Master's degree in mathematics before receiving his medical degree from the University of Chicago. He did his internship and residency in internal medicine at Yale University, studied at the Rockefeller Institute in New York, and completed his clinical training as a specialist in internal medicine at Columbia Presbyterian Medical Center in New York. He is board-certified in internal medicine and is a member of the Board of Governors of the American Board of Internal Medicine. Dr. Feinstein taught at the New York University School of Medicine from 1956 until 1962, and has been on the faculty of the Yale University School of Medicine since 1962, where he both teaches and treats patients (Feinstein, Tr. 16190–93; RX 279).

112. Dr. Feinstein has been consultant to government agencies, including the Food and Drug Administration and the Veterans Administration, involving problems in the design and interpretation of clinical trials or other forms of research dealing with the safety and efficacy of drugs. Dr. Feinstein has been Chief of the Research Support Center and the Cooperative Study Support Center at the West Haven Veterans Administration Hospital, a coordinating center for clinical trials conducted by the Veterans Administration. Dr. Feinstein also served as a member of the Veterans Administration Cooperative Study Evaluation Committee, which reviews proposed clinical studies for the Veterans Administration. Dr. Feinstein has been a member of the FDA Biometric and Epidemiology Advisory Commit-

tee, which reviews clinical studies submitted to the FDA to decide whether those studies were appropriately designed and conducted (Feinstein, Tr. 16193–94, 16199–200; RX 279).

113. Dr. Feinstein is one of about 300 invited members of the prestigious Association of American Physicians. He is an invited member of both the American Society of Clinical Investigators and the American Epidemiological Society. He is a member of the Institute of Medicine, a Fellow of the American College of Physicians, and a member of the Institute of Statisticians. He is also a member of other professional and honorary societies in the fields of science and medicine (Feinstein, Tr. 16194–96; RX 279). Dr. Feinstein is a member of the editorial boards of several well-recognized publications in clinical medicine today, including *The Journal of Clinical Pharmacology and Therapeutics, The Journal of Chronic Diseases,* and *The Journal of the History of Medicine and Allied Sciences.* He also regularly reviews articles for approximately 30 other medical journals, and for the past ten years has written a **[39]** regular column for *The Journal of Clinical Pharmacology and Therapeutics* concerning the design and analysis of various aspects of clinical research, including clinical trials (Feinstein, Tr. 16196–98; RX 279).

114. Dr. Feinstein's research interests are in the areas of clinical epidemiology and clinimetrics and is considered a founding father of clinical epidemiology, which encompasses the quantification of diagnosis, prognosis and therapy (Feinstein, Tr. 16201–02; RX 279). His book *Clinical Biostatistics* deals with the "design and conduct of various aspects of clinical research with the architecture and design of different studies, whether they be clinical trials or other forms of research for the analysis" of medical and clinical data. Dr. Feinstein has written many papers on methodology of clinical trials, including articles on methodology, statistics, randomization, placebos, and controls. His curriculum vitae contains 191 primary publications, including two books and several chapters in standard medical texts, 81 secondary papers, 100 abstracts, numerous book reviews, letters to the editor and editorials (Feinstein, Tr. 16203–06). His numerous articles dealing with the issue of randomized controlled clinical trials include: "Should Placebo-Controlled Trials be Abolished?", *European Journal of Clinical Pharmacology,* Spring, 1980: "On Standards for Publication of Therapeutic Research", *The Journal of Chronic Diseases,* Vol. 33 (1980); "The Need for Humanized Science in Evaluating Medication"; *The Lancet,* August 22, 1972 (RX 279).

William S. Fields, M.D.

115. Dr. William Fields is an expert in the areas of neurology and clinical testing (Fields, Tr. 16558, 16573; RX 262). He is Professor and,

since 1973, Chairman of the Department of Neurology at the University of Texas Medical School in Houston. Dr. Fields is a Diplomate of the American Board of Psychiatry and Neurology, certified in neurology. For certification in the neurology specialty, he had additional training in the area of psychiatry (Fields, Tr. 16519, 16524–25; RX 262B).

116. Dr. Fields holds an A.B. degree from Harvard College and an M.D. degree from Harvard Medical College. He had postgraduate clinical training at National General Hospital, Vanderbilt University, Nashville, Tennessee, at the Children's Memorial Hospital in Montreal, Canada, the Royal Victoria Hospital, and Barnes Hospital, St. Louis, Missouri. He also did research at the Montreal Neurological Institute and was a Rockefeller Fellow in Neuropsychiatry at Washington University School of Medicine (Fields, Tr. 16520–21, 16524; RX 262A).

117. After completing his formal education, Dr. Fields became an Associate Professor of Neurology in 1949 at Baylor College of Medicine in Houston, Texas, was Professor of [40] Neurology at that college from 1951 through 1967, and became Chairman of the Neurology Department of Baylor from 1959 through 1965. Subsequently, Dr. Fields became Professor of Neurology at the University of Texas Southwest Medical School in Dallas. In 1970 he became Professor of Neurology at the University of Texas Medical School (Fields, Tr. 16525–26; RX 262B).

118. At the time Dr. Fields was connected with Baylor, he was Chief of Neurology at the Methodist Hospital, the City/County Hospital, Ben Taub General Hospital, and the Veterans Administration Hospital. Dr. Fields has also been a Consulting Neurologist at Hermann, St. Luke's, Texas Children's and Diagnostic Center Hospitals, all in Houston, Texas. From 1956 until present, Dr. Fields has been the consulting neurologist for the Air Force Hospital at Lackland Air Force Base. While Dr. Fields was connected with the University of Texas Southwest Medical School at Dallas, he was the Senior Attending Neurologist at Parkland Memorial Hospital, and Presbyterian Hospital in Dallas, and a consultant in neurology at St. Paul Hospital and Baylor University Medical Center in Dallas (Fields, Tr. 16526–28; RX 262C). When Dr. Fields returned to Houston to become Chairman of the Department of Neurology at the University of Texas Medical School in Houston, he also became the Chief of Neurology Service at St. Anthony's Center, a position he held until 1979. In 1973 he became Chief of Neurology Service, a position he still holds, at Hermann Hospital (Fields, Tr. 16528–29; RX 262C). Dr. Fields has been the Chairman of the Committee for the Protection of Human Subjects (also known as the Institutional Review Board) at the University of

Texas Health Science Center since its inception. The Committee is charged with responsibility for reviewing proposed clinical research at the University (Fields, Tr. 16533).

119. Dr. Fields has done extensive work in the area of clinical testing, including clinical tests on an investigational new drug ("IND") relating to treatment of headache, and the testing of a drug containing caffeine as a headache remedy. He has also been connected with the NIH Stroke Study ("AITIA" Study), a 10-center clinical trial to determine whether aspirin may help prevent stroke, sponsored by the National Institute of Heart, Lung and Blood Diseases ("NIHL&B"). Dr. Fields was overall coordinator of this study. As a result of this multicenter clinical study ("AITIA" Study), the FDA authorized the use of aspirin for the prevention of strokes in males. Dr. Fields has been associated with subsequent aspirin trials sponsored by the NIHL&B (Fields, Tr. 16536–52).

120. Dr. Fields was a consultant to the Social Security Administration from 1966 to 1976, and was a member of the Veteran's Administration Advisory Committee for Psychiatry, Neurology and Psychology Service from 1966 to 1974 (Fields, Tr. 16532; RX 262E). He is a member of numerous professional societies, including the American Neurological Association, the American Academy of Neurology, the Association for Research of [41] Nervous and Mental Diseases, the American Association of Neurology Surgeons, and the Association of University Professors of Neurology (Fields, Tr. 16531; RX 262C–D). Dr. Fields has published more than 175 learned articles and books in the area of neurology and nervous system, which includes pain and headaches (Fields, Tr. 16553, 16555–58; RX 262H–V).

Leonide Goldstein, M.D.

121. Dr. Leonide Goldstein is an expert in the area of the biological basis of human behavior, including electroencephalogram ("EEG") testing and analyses (L. Goldstein, Tr. 17724). Biological basis of human behavior involves consideration of the brain in terms of the kind of phenomena which takes place within the tissue that can be explained by biochemical changes, electrical changes or other ways which relate to the actual tissue or organs which are part of the brain (L. Goldstein, Tr. 17748–49). By education, training and experience, Dr. Goldstein is a well-qualified expert in this area.

122. Dr. Goldstein is a Professor in the Department of Psychiatry, College of Medicine and Dentistry at New Jersey State University Medical School. He is also a Professor in the Graduate School of Applied and Professional Psychology at Rutgers University. Most of Dr. Goldstein's responsibilities at the medical school involve work with electroencephalogram waves, referred to as EEG's. Dr. Goldstein

is the Director of the Quantitative Electroencephalograph Laboratory at the medical school. The work of this laboratory exclusively involves studies with humans (L. Goldstein, Tr. 17726–30; RX 267).

123. In addition to teaching, Dr. Goldstein conducts an extensive amount of research which occupies approximately 60 percent of his time. His principal research interest has been the study of the brain, to determine the relationship between brain functions, as manifested by quantitative EEG patterns, and behavioral states. In this area, he has done EEG testing on approximately 1,000 to 1,500 human subjects, and has tested more than 100 drugs or compounds to determine their effect on the brain, using both normal and mentally ill subjects. His EEG work has included various psychotropic drugs, such as stimulants, hallucinogenics, sedatives, sleep inducers and antidepressants, as well as analgesics including Bayer Aspirin (L. Goldstein, Tr. 17735). Dr. Goldstein's scientific publications exceed 190 in number (L. Goldstein, Tr. 17732–40; RX 267C–P).

124. Dr. Leonide Goldstein is a member of a number of professional societies, including the Society for Neurosciences, Society for Biological Psychiatry, the Association for the Psychophysiological Study of Sleep, American Statistical Association, and Fellow of the American College of Neuro[42]psychopharmacology. Dr. Goldstein is the editor-in-chief of the peer review journal, *Research Communications in Psychology, Psychiatry and Behavior* (L. Goldstein, Tr. 17731–32; RX 267B). Dr. Leonide Goldstein holds a Bachelor of Arts degree, a Master of Arts degree from Amherst College, and a Doctorate degree from the Sorbonne, University of Paris, Paris, France. Positions held by Dr. Goldstein include Associate Professor of Pharmacology at Emory University in Atlanta, Neuropharmacologist with the New Jersey Neuropsychiatric Institute in Princeton, and a visiting professorship at Princeton University (L. Goldstein, Tr. 17730–31; RX 267A).

Theodore Horner, Ph.D.

125. Dr. Theodore Horner is an expert in biometry, which is the application of statistical and mathematical methods to biological problems (Horner, Tr. 10735–43). Dr. Horner received a Ph.D. in Experimental Statistics from North Carolina State University. He is presently a consulting statistician in the area of applied statistics, with a primary interest in problems relating to biology and medicine. He has worked extensively with clinical trials, evaluations of pharmaceutical preparations, animal studies, toxicity studies, and other biometrical work. He has done consulting work for Abbott Laboratories, Hazelton Laboratories, and Litton Bionetics Laboratories, among others. Prior to becoming an independent consultant, Dr.

Horner was a principal scientist with Booz, Allen Applied Research, working with the application of statistics to biological defense problems. He has done consulting work for the Food and Drug Administration and the Federal Trade Commission (Horner, Tr. 10735–43, 10908; RX 282).

126. Dr. Horner taught statistics for four years at Iowa State University, and has taught operations research at Vanderbilt University. He is a member of the Institute of Mathematical Statistics, the American Statistical Association, and the American Society for Clinical Pharmacology and Therapeutics. He is a former Secretary-Director of the Eastern North American Region of the Biometric Society, an international organization (Horner, Tr. 10735–43; RX 282).

127. Dr. Horner has written numerous published and unpublished reports relating to biostatistics and biometrics (Horner, Tr. 10735–43; RX 282).

Christopher Rhodes, Ph.D.

128. Dr. Christopher Rhodes is a pharmaceutical scientist with expertise in the formulation and processing of drug products and their evaluation. Dr. Rhodes is Professor and Chairman of the Department of Pharmacy at the School of Pharmacy of the University of Rhode Island. He received a Bachelor of Pharmacy degree with honors from the University of London, [43] England, and Ph.D. for work concerning the physico-chemical properties of drug systems. Dr. Rhodes then pursued a course of post-doctoral study at Purdue University, under the direction of Dr. Gilbert S. Banker in the area of the design and evaluation of new dosage forms. He was formerly an Associate Professor at the State University of New York at Buffalo (Rhodes, Tr. 11048; RX 259).

129. Dr. Rhodes has taught undergraduate and graduate students of pharmacy research in the areas of formulation and dosage form design. He has performed clinical research in collaboration with medical doctors on several occasions. His research has concerned the design and evaluation of dosage forms, and the link between dosage form design and clinical response (Rhodes, Tr. 11050–52).

130. Dr. Rhodes' present research involves dosage form design, particularly with respect to the formulation and evaluation of compressed tablets in terms of biological availability or clinical trials. One of Dr. Rhodes' current projects involves research on new excipients in aspirin tablets. Dr. Rhodes is a pharmaceutical consultant to companies in North America and Western Europe, and is often invited to give lectures to professional groups of pharmacists and physicians, including government groups. He is an advisor to a number of government agencies, including the World Bank and the Population Council.

Dr. Rhodes is involved in research with scientists at the Brown University Medical School, and holds a scientific appointment at Roger Williams Hospital in Providence, Rhode Island, where he is working on the design and interpretation of clinical trials. He has lectured to medical students at Brown University on drug product selection and the role of biopharmaceutics and clinical performance. Dr. Rhodes has received grants from numerous pharmaceutical companies and from the National Institutes of Health (Rhodes, Tr. 11055–57; RX 259).

131. Dr. Rhodes has published two pharmaceutical texts and 110 scientific articles, 105 of which have appeared in peer-reviewed scientific journals. He is editor of the *Journal of Drug Development and Industrial Pharmacy* and has been invited to lecture to Food & Drug Administration (FDA) inspectors on a variety of topics (Rhodes, Tr. 11057–59; RX 259).

132. Dr. Rhodes has written articles and performed research relating to the properties and actions of salicylic acid (Rhodes, Tr. 11072–73; RX 259).

133. Dr. Rhodes is a member of the Academy of Pharmaceutical Sciences Regulations and Standards Committee. He is also a Fellow of the American Pharmaceutical Association, and a member of the Rhode Island Pharmaceutical Association, the American Association of Colleges of Pharmacy, the American [44] Association of University Professors, the Kappa Psi Pharmaceutical Fraternity, and the Sigma Xi Scientific Honorary. Dr. Rhodes also serves as a member of the United States Pharmacopoeic Convention and is a member of the United States Pharmacopeia Pharmaceutical Chemistry Committee, which is charged with evaluating the various official formulations (Rhodes, Tr. 11097–98, 11100; Banker, Tr. 12523–27).

Barrett Scoville, M.D.

134. Dr. Barrett Scoville, a former Director of the FDA's Division of Neuropharmacological Drug Products, is familiar with FDA practice and procedure relating to the regulation of drugs (Scoville, Tr. 14323, 14336).

135. The first position held by Dr. Scoville with the Food and Drug Administration, commencing in 1969, was that of Medical Officer in the Division of Neuropharmacological Drugs of the Bureau of Drugs. He had held this position for less than one year when he was promoted to the Deputy Director of the division. Dr. Scoville remained Deputy Director until 1973. He then advanced to Acting Director of the division in 1973–1974, and became Director of the division for the period 1974–1976 (Scoville, Tr. 14310–11, 14313–14; RX 266B).

136. The Neuropharmacological Division of the Bureau of Drugs of

the FDA was responsible for the safety and efficacy of drug products used for neurology, psychiatry and analgesia. The drugs regulated by this division included aspirin. The division was responsible for all prescription drug products falling in these categories, and until 1974 or 1975, was also responsible for regulating over-the-counter drug products in these categories (Scoville, Tr. 14311–12, 14322, 14329).

137. While employed by the FDA, Dr. Scoville was a member of the Medical Evaluation Committee. This Committee was concerned with compliance with FDA regulations in the marketplace and made decisions as to what action should be taken against defective products, such as recall. Dr. Scoville was also a member of the Medical Officer Review Format Committee, which was concerned with defining standards and procedures for Bureau of Drug personnel responsible for reviewing clinical data (Scoville, Tr. 14315–16, 14335; RX 266B).

138. Dr. Scoville was a member of the IND-NDA Task Force of the Bureau of Drugs (Scoville, Tr. 14316; RX 266B). IND refers to "investigational new drug application" and NDA refers to "new drug application". The IND is submitted to obtain permission for human testing of a new drug not yet authorized for marketing. The NDA is the application for approval to market a new drug. The Task Force had responsibility for developing better organization and guidelines for these processes. Members of the Task Force had a thorough understanding of the various [45] requirements and procedures for IND and NDA approvals. Dr. Scoville was also a member of the FDA's Committee on Evaluating Antidepressant Drugs, which had responsibility for developing testing guidelines (Scoville, Tr. 14317–18; RX 266B).

139. Dr. Scoville was an official spokesman for the FDA and as such participated in panels, symposia and seminars in which FDA practice and procedure was explained to experts and to the general public (Scoville, Tr. 14318–19; RX 266).

140. After leaving full-time employment at the FDA in 1976, he remained a consultant with the FDA until 1978 and a consultant to the National Institute of Neurological and Communicative Disorders and Stroke until 1979. He has continued to give lectures, participate in seminars and symposia with drug experts, and write articles dealing with FDA drug regulations (Scoville, Tr. 14320–21; RX 226D–F).

3. Respondent's Company Witnesses

George Goldstein, M.D.

141. Dr. George Goldstein is an expert in the area of the use, efficacy and safety of Sterling Drug analgesic products: Bayer Aspirin, Bayer Children's Aspirin, Cope, Vanquish and Midol, including the ingredients contained in those products (G. Goldstein, Tr. 14744, 14783; RX

274). Dr. Goldstein came to Sterling in January 1975, as Medical Director of Sterling's Glenbrook Laboratories division in January 1975, succeeding Dr. Robert John, who testified as a complaint counsel witness in this proceeding. Glenbrook Laboratories is the division of Sterling principally concerned with nonprescription drugs, including the analgesic products involved in this matter (G. Goldstein, Tr. 14724–25; RX 274A–B). The Medical Director of Glenbrook Laboratories is the highest medical position in Glenbrook (G. Goldstein, Tr. 14738).

142. Since January 1, 1979, Dr. George Goldstein has been Vice President and Medical Director of Winthrop Laboratories, the division of Sterling concerned principally with prescription drugs. His duties involve the supervision of all medical activities, including research and development, for all products manufactured by Winthrop Laboratories. The prior position held by Dr. Goldstein was that of Director of Regulatory Affairs for Sterling. His duties included liaison for all divisions of Sterling with the United States Food and Drug Administration and the Consumer Product Safety Commission. Dr. Goldstein assumed this position on January 1, 1977 and remained in it until becoming Vice President of Winthrop on January 1, 1979 (G. Goldstein, Tr. 14722–23; RX 274). Prior to becoming Director of Drug Regulatory Affairs in January 1977, Dr. Goldstein was a Medical Director of Glenbrook Laboratories, commencing in January 1975, and in January 1976 he became the [**46**] Vice President of Glenbrook Laboratories, as well as its Medical Director.

143. While with Glenbrook Laboratories, Dr. Goldstein was responsible for supervision of all scientific and medical aspects of the products manufactured by Glenbrook which included substantiation for advertisements for those products. Responsibility for substantiation encompassed both medical and pharmaceutical issues. As part of his duties, Dr. Goldstein kept abreast of current scientific literature and developments in the analgesic area (G. Goldstein, Tr. 14722, 14725–27).

144. As part of his duties as Medical Director of Glenbrook Laboratories, Dr. Goldstein was designated in 1975 by respondent Sterling as medical liaison to respondent's attorneys in this matter (G. Goldstein, Tr. 14742).

145. Dr. Goldstein has served on a number of committees within Sterling. One such committee is the Medical Research Committee which reviewed protocols for testing of drugs already on the market. He was also a member of the New Drug Committee which reviewed protocols for testing of any new drug (G. Goldstein, Tr. 14738).

146. Dr. Goldstein holds a Bachelor of Arts degree from Columbia University and an M.D. degree from the State University of New

York, College of Medicine at Syracuse. The bulk of Dr. Goldstein's post-graduate clinical training and practice was in the field of Pediatrics. He interned at Baltimore City Hospital and then served in the United States Air Force where he was Chief of the Pediatric Service and Chief of the Pharmacy Service of the 864th Medical Group. After completion of his military service, Dr. Goldstein was a resident in pediatrics at New York Hospital, Cornell Medical Center. Thereafter, he was in private practice for 12 years. While in private practice, Dr. Goldstein was connected with the Phelps Memorial Hospital where he was Deputy Director of Pediatrics and Chairman of the Pharmacy and Therapeutics Committee for a number of years. He was also an instructor in Pediatrics for approximately eight years at the New York Medical College (G. Goldstein, Tr. 14739–40; RX 274).

147. Dr. Goldstein is a Diplomate of the National Board of Medical Experts, certified by the American Board of Pediatrics, a member of the American College of Clinical Pharmacology, and a Fellow of the American Academy of Pediatrics (G. Goldstein, Tr. 14741; RX 274B).

James Alberts

148. James Alberts is Vice President and Director of Marketing and Advertising Services, Sterling Drug. His responsibilities include advertising, trade promotion, public relations, consumer response, and marketing research (Alberts, [47] Tr. 8913). Mr. Alberts has been with Sterling for 20 years and has worked there in various capacities in the areas of advertising and marketing. Mr. Alberts started as a product manager. During the period from 1969 to 1974, Mr. Alberts was a group product manager for Bayer Aspirin, Bayer Children's Aspirin, and Cope. He had no responsibility for Vanquish until he became Director of Marketing in 1977 (Alberts, Tr. 8914–16, 9018). As part of his job, Mr. Alberts has kept informed about the marketing positions of Bayer Aspirin, Bayer Children's Aspirin, Vanquish, and Cope which includes information on sales, market trends, consumer and research marketing and competitive advertising (Alberts, Tr. 8917–18).

Morris Auerbach

149. Morris E. Auerbach testified by deposition, due to age and ill health. He was deposed through written questions by respondent and oral cross-examination by complaint counsel. The written questions, answers and transcript of the cross-examination were introduced into evidence as RX 286.

150. Mr. Auerbach graduated in 1928 from New York State College for Teachers, receiving a Bachelor of Arts degree in English and Chemistry (RX 286B). He has no educational background, training, or

experience in the fields of medicine, toxicology or pharmacology (RX 286C). Mr. Auerbach was employed by Sterling Drug, Inc. from 1928 until he retired in 1969. He was hired as an assistant chemist and in the early 1940's he became Supervisor of the analytical laboratory at the Sterling-Winthrop Research Institute, a position he held until he retired (RX 286C).

151. Mr. Auerbach served in an individual capacity on several committees of the United States Pharmacopeia. He was not a representative of Sterling, nor any of its subsidiaries and aspirin was not one of the drug substances assigned to him. Dr. Klumpp was the official spokesperson on medical matters for Sterling and its subsidiaries during this time. Mr. Auerbach did submit comments regarding chemical testing and controls for aspirin to the USP in response to solicitations from Lloyd Miller, USP Director of Revision. These comments were not subject to review or authorization by Sterling (RX 286C–E).

Richard K. Hartman

152. Richard K. Hartman, presently an Account Supervisor at Thompson-Koch Advertising Agency, a wholly owned subsidiary of Sterling, has had responsibility for Midol advertising since 1964 in his positions as Account Supervisor and Account Executive (Hartman, Tr. 9135).

E. Clifford Hall

153. E. Clifford Hall was employed at Sterling from 1966 to 1977, as a Product Manager and Group Product Manager. As [48] Product Manager, Mr. Hall was responsible for Vanquish, Phillip's Milk of Magnesia, Campho-Phenique, and Haley's MO. He was Product Manager for Vanquish from 1969 to 1975. During that time, Benton & Bowles and Lois-Holland-Calloway were advertising agencies that worked on the Vanquish account. Mr. Hall was the principal contact at Glenbrook Laboratories with these advertising agencies during that period of time. Mr. Hall is presently employed at the Schering-Plough Corporation as Marketing Manager for International Operations (Hall, Tr. 9206–07).

Theodore Klumpp, M.D.

154. Dr. Theodore Klumpp testified by deposition, due to age and ill health, on behalf of respondent Sterling (Klumpp-RX 285). During the 1960's, Dr. Klumpp was the official spokesperson for respondent on medical and scientific matters (Klumpp-RX 285L). Dr. Klumpp has a Bachelor of Science degree from Princeton University and an M.D. degree from Harvard (Klumpp-RX 285Z034). Apart from positions at

Sterling, Dr. Klumpp has held positions as Assistant Clinical Professor of Medicine at Yale University Medical School, Chief Medical Officer of the Food and Drug Administration, Chief of the Drug Division of the Food and Drug Administration, and Director of the Division of Drugs, Food and Physical Therapy of the American Medical Association (Klumpp-RX 285E, RX 285Z34). Dr. Klumpp was elected Vice President and a Trustee of the United States Pharmacopeia Convention in 1950 and was re-elected in 1960 (Klumpp-RX 285E-F).

155. In 1942, Dr. Klumpp joined respondent Sterling as President of the subsidiary that became known as Winthrop Laboratories. Winthrop Laboratories deals principally with prescription drugs. Dr. Klumpp remained President of Winthrop Laboratories until 1970 (RX 285Z34). Dr. Klumpp also held the position of a Director of Sterling Winthrop Research Institute from 1950 until his retirement in 1973 (RX 285G). Dr. Klumpp, from 1960 until 1973, was also a member of the Board of Directors and Vice President of Sterling (Klumpp-RX 285E–H, RX 285Z34, RX 285Z53).

Edward Mannix

156. Edward Mannix is a coordinator for contract packagers at the East Greenwich plant of Sterling's Winthrop Division located near Rensselaer, New York. From 1939 to 1976, he was associated with the Glenbrook Division of Sterling, where he was laboratory assistant, laboratory supervisor, Assistant to the Director of Quality Control, and in 1962 became Director of Quality Control of the Trenton operation, taking over that position from Jerome Winig, who became Plant Manager. [49] Mr. Mannix left the Trenton plant in 1976 to work at the Winthrop Laboratories Division of Sterling in Rensselaer, New York. His initial position at Rensselaer was laboratory manager, and his responsibilities involved directing the operation of the control laboratories there (Mannix, Tr. 14603–04).

Gerard Mattimore

157. Gerard Mattimore is Group Marketing Director at Glenbrook Laboratories. He is responsible for marketing Sterling's nonanalgesic products, including Phillip's Milk of Magnesia and Diaperene Baby Products. He has been employed at Sterling since 1962, when he started as a salesman. From 1963 to 1968, Mr. Mattimore was in sales management, from 1968 to 1976 he was in product management, and from 1976 to 1977 he was in product management, and from 1976 to 1977 he was Director of Marketing Services (Mattimore, Tr. 15334–35).

158. In 1967 and 1968, Mr. Mattimore was Director of Sales Administration and Sales Administration Manager at Glenbrook

Laboratories, where his responsibilities included dissemination of all instructions and information to the field sales force of approximately 100 sales representatives. The great majority of communications to the sales force were initiated by Mr. Mattimore, who was the primary source for sales-related information. Mr. Mattimore was familiar with the system of distribution of Bayer Aspirin and other brands of aspirin and analgesic products (Mattimore, Tr. 15336).

Maurice Tainter, M.D.

159. Dr. Tainter joined Sterling in 1943 as Director of Research, and held this position until 1969. Dr. Tainter was founding director of Sterling-Winthrop Research Institute, a drug research institute at Rensselaer, New York (1946–1960). Dr. Tainter was also a vice-president of Sterling from 1946 to 1969. In 1960, Dr. Tainter became vice-chairman of the Sterling Research Board, and, as Director of Research, had responsibility for a research staff of 700. His duties included research and policy matters, as well as research for new products (RX 284C–E, RX 271).

160. Dr. Maurice Tainter received an A.B. in 1921 and an A.M. in 1924 and an M.D. in 1925 from Stanford University in California (RX 284B–C, RX 271). Dr. Tainter is the author of approximately 250 publications in the fields of medical and dental pharmacology, therapeutics, toxicology, research administration, and the history of medical research. Dr. Tainter has been on the editorial boards of various medical and pharmacologic journals, including *Clinical Medicine, Pharmacological Reviews* and *Toxicology and Applied Pharmacology* (RX 284B–C, RX 271). Dr. Tainter is a member of a number of **[50]** professional organizations, including the New York Academy of Sciences (President, 1955), the American College of Clinical Pharmacology and Chemotherapy (Charter Member and Fellow), the American Physiological Society, and the American Society for Clinical Pharmacology and Experimental Therapeutics (RX 284B–C, RX 271). Prior to joining Sterling, Dr. Tainter held professional academic positions in the Department of Pharmacology at Stanford University Medical School (1925–1943), and was head of the Physiological Sciences Department in the College of Physicians and Surgeons Dental School, San Francisco (1940–1943) (RX 284B–C, RX 271).

161. Dr. Tainter has been qualified as an expert in court and has testified at congressional proceedings (RX 284E–F; RX 271).

Monroe E. Trout, M.D.

162. Dr. Monroe E. Trout, Senior Vice President of Medical and Scientific Affairs at Sterling, has been employed by Sterling since 1968. He was elected Senior Vice President in 1978. Prior to that time,

he held various positions with the company, including Medical Director and Vice President of Winthrop Laboratories, Medical Director of Sterling U.S.A., Medical Director of Sterling Drug, and Corporate Vice President of Medical Affairs (Trout, Tr. 16078–79). Dr. Robert John, Medical Director of Glenbrook Laboratories from 1971 to 1974, reported to Dr. Trout (Trout, Tr. 16084).

163. Prior to joining Sterling, Dr. Trout practiced medicine for seven years, both in the U.S. Navy and as Chief of Medicine at a large state hospital in Harrisburg, Pennsylvania. He also worked for Pfizer, Inc., in their Regulatory Affairs Department and as Assistant to the Vice President for Pharmaceuticals (Trout, Tr. 16079–80).

Jerome Winig

164. Jerome Winig worked for Sterling for 42 1/2 years prior to his retirement in August 1977. He joined Sterling in 1935 as a Bench Chemist. In 1943, he became Chief Control Chemist. After helping design the new plant in Trenton, Mr. Winig was promoted to Director of Quality Control in 1947. In 1960 he became Assistant Plant Manager, and in 1962, Plant Manager. In 1967 Mr. Winig became Vice President of the Glenbrook Laboratories Division of Sterling. In 1970, he was promoted to Divisional Vice President for Manufacturing of Sterling, and retained this position until his retirement in 1977 (Winig, Tr. 13614).

165. As Director of Quality Control and Chief Control Chemist, Mr. Winig's responsibilities involved approving or rejecting material used in the manufacture of Bayer Aspirin. He [51] was also responsible for approval of all outgoing shipments. When he became Plant Manager, Mr. Winig relinquished responsibility for quality control. Edward Mannix became Quality Control Director at that time (Winig, Tr. 13617). As Vice President of Glenbrook Laboratories, Mr. Winig was responsible for five manufacturing plants (Winig, Tr. 13618).

166. During his entire tenure at Sterling, Mr. Winig had responsibilities and duties associated with Bayer Aspirin. He also helped to design the Bayer Aspirin plant in Trenton. The design of that plant involved many advances in manufacturing processes and standards. It took about six years to develop equipment for the new plant (Winig, Tr. 13619). Mr. Winig was responsible for the development of the formula and manufacturing process for Bayer Children's Aspirin in the late 1950's (Winig, Tr. 13619). During his tenure at Sterling, Mr. Winig was fully familiar with the manufacturing processes and quality control procedures at the Trenton plant (Winig, Tr. 13620).

167. Mr. Winig is a member of the American Chemical Society, the American Pharmaceutical Association, the American Institute of Chemists, the Academy of Pharmaceutical Sciences, the Society for

the Advancement of Management in the United States, and the Manufacturing Controls Committee of the American Proprietary Association. Mr. Winig became active on the Manufacturing Controls Committee of the American Proprietary Association in 1965 by invitation. On that committee, he worked closely with the Food and Drug Administration in designing procedures and changes in drug manufacturing practices. The committee included Mr. Winig's counterparts at other companies and other management and manufacturing personnel.

III. RESPONDENTS MADE THE ADVERTISING REPRESENTATIONS ALLEGED IN THE COMPLAINT

A. *The Meaning of Advertisements*

168. In determining whether an advertisement made a particular representation, the appropriate standard to be applied is whether, taking the advertisement as a whole, the representation constitutes one reasonable interpretation of the advertisement which some consumers may reasonably understand the advertisement as making.

169. The primary evidence with respect to the meaning of advertisements in the record consists of the advertisements themselves.

170. The record also contains secondary evidence regarding the meaning of advertisements, including:

(a) The expert testimony of Drs. Ivan Ross, Timothy Brock, Virginia Miles, and Russell Haley. **[52]**

(b) The copy test data from the Zeisel Copy Tests (CX 520), the Burke "Day After Recall" Tests (CX 441, 442, 451 and 452) and the "ASI Audience Reaction Tests" (CX 567 and 568) and, to a limited extent, some verbatim comments of consumers in response to comprehension and recall questions reported therein.

(c) Certain consumer studies regarding consumer understanding of some attributes of OTC internal analgesic products, such as effectiveness, safety, strength and speed (CX 404, 440).

171. In arriving at a determination of whether respondents' advertisements in the record made the representations as alleged in the Complaint, I have primarily and in the first instance relied on my own judgment based on my knowledge and experience in interpreting the meaning of each advertisement separately. I further relied on secondary evidence as confirmation of my conclusions. I have not relied on secondary evidence when, after careful study and reflection, I found it unpersuasive and inconsistent with my initial determinations. In this connection, I have focused on what appears in each advertisement in terms of its audiovisual contents, and disregarded the so-

called advertising campaign themes and other extraneous information not contained in an advertisement.

172. Among the various kinds of data which are useful in determining the message that consumers take from a particular advertisement are copy tests. These tests are generally conducted with respect to a particular advertisement or advertisements shortly after respondents have viewed them. The object of such tests is to collect data from those surveyed regarding their impressions of the content or the meaning of such advertisements.

1. The ASI Audience Reaction Tests (CX 567, CX 568)

173. The ASI Audience Reaction Tests received into evidence as CX 567 and CX 568 were conducted by Audience Studies, Inc. (ASI) on television advertisements for Bayer Aspirin. The tests were of standardized design. The purpose of these surveys was to measure the effectiveness of one advertisement in comparison to the effectiveness of other advertisements for products in the same category (CX 567, CX 568, CX 638B).

174. The stipulated testimony of Gerald Lukeman, President of ASI, concerned the mechanics of conducting Audience Reaction [**53**] Tests (CX 638). ASI's principal line of business is the measurement of communication in one form or another. Since 1961 most of ASI's work has involved the measurement of television and print advertising, network pilot program material, and motion pictures. ASI offers various testing services including the "theatre" system or "Audience Reaction Test," the use of cable television for "on-air" testing, and the miniature supermarket system.

175. ASI has, throughout the period that is relevant in this case, utilized standardized procedures in (1) selecting respondents to participate in Audience Reaction Tests and (2) conducting such tests and processing the data collected therein. Such standardization is called for by the nature of the service which ASI offers clients for whom it tests television commercials: the ability to compare the results of a test of one commercial with the results of tests conducted on others for products in the same category. Thus, while there have been minor modifications in the methods used over time, as indicated below, the basic procedures have remained essentially the same and were followed in CX 567 and 568 (CX 638B).

176. The audiences which viewed the advertisements reported upon in CX 567 and 568 were recruited from the Los Angeles metropolitan area. Recruitment was accomplished, in part, by in-person contact in high traffic areas, such as shopping centers. The different shopping center locations where such recruiting occurred were chosen in an effort to secure a sample that reflects the differing geographic and

socio-economic characteristics within that metropolitan area. Recruiting quotas were based on the characteristics of age and sex. Audiences are generally recruited so as to provide an approximately 50/50 sex distribution and to secure approximately half of the respondents below age 35 and half above age 35 (CX 638B).

177. In-person recruiting was supplemented by telephone calls using a central telephone facility. This supplemental telephone call recruiting was accomplished through the use of "reverse" directories which list people by their addresses. These were used to foster the best possible geographic and socio-economic dispersion of those ultimately recruited (CX 638C).

178. The ASI standard sampling procedures were designed to produce a sample whose age, sex and socio-economic characteristics are comparable to samples previously recruited and tested by ASI (CX 638C).

179. ASI recruiters were instructed to inform potential respondents that they were being invited to preview network television programs. They were not to be told about ASI. If respondents asked for an explanation as to why there was no charge for the program, recruiters were instructed to tell them [54] that they would be asked for their opinions about the material they would see (CX 638C).

180. Upon arriving at the ASI testing facility, according to ASI's standard procedure, certain respondents were selected by ASI personnel to operate the dials of a recording machine at their seat designed to measure their reactions to the materials they were to view. A second subsample was selected for the test reported in CX 567 to participate in a "focus group" discussion held at a point in the evening after the commercials had been viewed (CX 638C–D, CX 567 at pp. Z005–Z013).

181. After the ASI employees completed the subsample selections, the ASI standard procedure called for the respondents to be seated in a theater and asked to fill out a classification questionnaire requesting various demographic and product usage/preference information. This questionaaire also asked respondents to select products from various product categories which they would desire to win as a prize (a pre-exposure selection measure). An example of the classification, demographic and pre-selection questions is to be found in CX 567, pages Z020 through Z024 (CX 638D).

182. ASI generally recruited more respondents than were required for its 250 person standard sample. Thus, approximately 350 people—on an average—participated in a typical ASI test evening. Thereafter, the responses of certain respondents, whose age, sex or other socio-economic characteristics were over-represented in the audience, were eliminated by a randomized process (CX 638D).

183. Following collection of the classification and pre-selection questionnaires, the audience was shown a "control" cartoon which had been used as a standard for most ASI sessions. Use of the "control" cartoon was designed to permit those in the segment of the audience to learn to manipulate their dials; it was also designed to permit ASI employees to compare this audience's dial reactions to the same material (the same "control" cartoon) reacted to by many other audiences. If the audience's reactions to the "control" cartoon did not satisfy ASI that this audience was reacting in reasonable accord with norms based on past audiences' reactions, the data generated through the subsequent questionnaire regarding "program" material would be discarded and that program material retested at a later date (CX 638D).

184. Following the "control" cartoon, a television program was shown to the entire audience. Those with dials reacted to the program by manipulating the dials, and at the conclusion of the television program all audience members were asked to fill out a questionnaire about the program. It is ASI's practice not to include the results of this questioning in its reports (CX 638E). **[55]**

185. After the television program was shown, the audience was told that it would be seeing a series of five commercials ("commercial" material) and a five-section commercial questionnaire booklet was distributed. Then the first commercial was shown. As with the "control" cartoon, the first commercial is always a "control" (*i.e.,* a commercial tested many times previously for which audience reaction is known). As with the "control" cartoon, ASI monitored the audience's reaction to the first "control" commercial to determine if it was reacting within normal limits established through ASI's prior experience with reactions to the same commercial. If the audience's reactions to the "control" commercial did not satisfy ASI that this audience was reacting in reasonable accord with norms based on past audiences' reactions, the data generated through subsequent questionnaires regarding the "commercial" material would be discarded and that commercial material retested at a later date (CX 638E).

186. Following the showing of this first "control" commercial, the audience was asked to fill out the first section of its five-page questionnaire. Immediately thereafter the second commercial was shown, and the audience filled out the second section of the questionnaire (CX 638E). This procedure was followed until all five commercials were shown and all five sections of the questionnaire was completed (CX 638E–F).

187. After the five commercials, the audience was shown a second television program segment and filled out a short questionnaire regarding it (CX 638F).

188. Thereafter, the audience was told that the pre-selection preference questionnaire was the incorrect one. A "correct" prize selection questionnaire containing an additional product category was thereafter administered giving the audience a second chance to select the product from an available list that they would like to win as a door prize. This second, or "post-selection," prize questionnaire was then collected (CX 638F).

189. Finally, the audience was given a "recall questionnaire" which asked the audience to think back to the commercials they saw earlier and to write down the products and brand names and everything else they remembered about each commercial. This "recall questionnaire" (*e.g.,* CX 567 at p. Z025) was administered approximately 30 to 40 minutes after the commercials were viewed. After the "recall questionnaire" was collected, prizes were awarded and the evening was concluded (CX 638F).

190. The procedure outlined above applied to all members of the audience except for the group chosen earlier to participate in group discussions. This group, composed of 10 to 12 people, **[56]** was taken out of the theater after the commercials were aired and, in a session led by a trained ASI moderator, the group discussed, among other things, some or all of the commercials they had viewed. People were initially invited to participate in focus groups based upon the opinion of an ASI moderator that they were not nonverbal and, thus, would be willing to discuss their opinions of the commercials they viewed (CX 638G).

191. Responses to the open-ended questions asked in the various questionnaires were coded internally by ASI's coding department. That department consisted of a supervisor, one or two assistants, and a staff of coders. The supervisor's responsibility extended to assigning work to coders, checking the accuracy of coding and spotting problems that may exist in coding or in establishing coding categories. The assistants' responsibilities included checking and accuracy of coding and training coders.

192. Coding of open-ended responses to the "main idea of the commercial" question and the "recall" question began with the preparation of a recommended coding outline for each question. This outline was based upon a coder's review of the commercial itself, prior ASI reports on other commercials for the same product, and approximately half of all responses given to the particular question. The recommended coding outline was approved by the coding supervisor and then by the project director. ASI's policy is, as much as possible, to use the same codes over a period of time for advertisements for the same product in order to permit comparisons across tests. After the recommended outline of codes was approved by the project director, the

coder took each verbatim comment and coded it by placing it into what the coder thought was the appropriate category. The accuracy of coding was to be checked first by the coding supervisor. If a project was especially complex, or if questions or problems were encountered in the coding process, a project director's assistance was enlisted (CX 638H–I).

193. Coded open-ended responses together with closed-ended (or "check off" type) responses were sent to ASI's internal keypunching department where they were to be keypunched and processed by as computer. ASI's procedure called for all data to be "double-punched" so that the accuracy of keypunching could be verified. Keypunchers were hired only if they had at least two years' experience. Applicants were required to take at least two tests at ASI, one concerning visual speed and accuracy and the other on the keypunching machines themselves. Keypunchers thereafter hired were trained by ASI's keypunching supervisor (CX 638I).

194. After the keypunched data was fed into a computer, the computer's printout of coded responses was also checked, according to ASI's standard procedures, by the coding supervisor, the project director and ASI's department in charge of editing final reports prior to issuance (CX 638I). **[57]**

195. The computer printouts of all responses (open-ended) are checked by the computer operator before they are released from that department. Thereafter, all the computer-tabulated data are delivered to a project director who also checked on the accuracy of the data (CX 638I).

2. The Burke "Day After Recall" Surveys (CX 441, 442; CX 451–454)

196. The six "Day After Recall" tests received into evidence (CX 441, 442, 451, 452, 453, and 454) were conducted by Burke Marketing Research (Burke) for Glenbrook Laboratories and Thompson Koch on two Midol advertisements under challenge here ("Woods and Stream," CX 296(A): "Life", CX–296(B)) and for DFS on several Bayer advertisements, among them, three under challenge here ("Inside Story #1, CX 38; "Inside Story #2," CX 39; "Library," CX 18). These were communications tests primarily for the purpose of determining whether television commercials could be remembered a day after being seen on the air in their formal environment. These tests were not designed to be national probability tests (Granger, Tr. 4163; Lipstein, Tr. 12074). The tests were of standard design—Burke has conducted fifteen to twenty thousand such tests for nearly 25 years for package goods manufacturers of over-the-counter internal analgesics (Granger, Tr. 4163–34, 4166).

197. James Granger is the group vice-president for client and project services for Burke Marketing Research. Burke Marketing Research is a full-service custom marketing research company which (in addition to copy testing) conducts studies in the areas of product testing, concept testing, advertising evaluation and a variety of other services (Granger, Tr. 4163). CX 441 and CX 442 were compiled and reported by Burke while CX 451–454 were compiled and reported by DFS. However, Burke did the field work for all six tests (Granger, Tr. 4165–6).

198. Burke tests are run on adds which are actually aired, either nationally or in three or four selected geographically dispersed cities (Granger, Tr. 4166–8). In those three or four cities which are chosen for the test, selection of the subjects is done by random selection of phone numbers from local telephone directories (Granger, Tr. 4168–9).

199. The standard Burke questionnaire or a variation of the standard questionnaire was used in the six identified CX (Granger, Tr. 4173). The questionnaire in each of these tests first asked the subject if on the preceding night (s)he saw any part of the program segment in which the test ad was scheduled; if so, whether (s)he saw an ad for the test products' class of products (*e.g.*, "menstrual remedies" or "headache remedies") and if so what brand. If the correct brand was not mentioned up [58] to that point the subject was asked if during the program (s)he happened to see an ad for the test brand. Once the subject indicated (s)he recollected an ad for the test brand (s)he was asked to tell anything (s)he remembered about the test advertisement, what the commercial looked like, what it said, and what ideas about the product the ad brought out. Finally, subjects were asked what activity they were engaged in just before, during and after the time the ad was run, using prompts describing the program segments (Granger, Tr. 4173, 4175–7, 4180–1; CX 441R–U; CX 442L, Q; CX 452Z007; CX 4530, R; CX 454S, T). This latter activity question is used to determine the size of the commercial audience which in turn is the base on which the "related recall" score is calculated (Granger, Tr. 4176–7). The size of the commercial audience for each of these six Burkes in evidence was typical. For example, CX 442, with a 200 program audience quota, had a commercial audience size of 116, which was typical. Commercial audience sizes for the other Burkes was as follows: CX 441, 121; CX 441, 167; CX 452, 170; CX 453, 153, and CX 454, 153 (Granger, Tr. 4179).

200. Analysis of data in the six tests in evidence began with whether subjects claimed to have seen the test ads, ("claimed recall"), whether, first, in response to the brand category cue, or second, in response to the brand name cue (Granger, Tr. 4180–81). Then responses to the

questions calling for subjects to tell what the advertisement said are analyzed to determine if the verbatim responses related to what was actually in the ads ("related recall"). This data was broken out again on the basis of whether subjects were prompted by the brand category cue or the brand name, and was displayed on the basis of response codes of two major classes, whether related recall relates to sales message or situation visual (Granger, Tr. 4181–82). Finally, the verbatim responses to the questions asking what the ad said were reproduced, first, those verbatims included in related recall results and those not included in related recall results (CX 441F–K; 442F–K; 451–I–M, P–S, V–X, Z001–Z003; CX 452H–Q, T–Z; CX 453G–K; CX 454F–M).

201. Verbatim answers were recorded using a verbatim recording technique. The interviewer was trained in how to write out in long hand the narrative answer that the respondent gave to the open-ended questions that asked what the ad said. (Granger, Tr. 4172–74). Interviewers engaged in probing questions such as "what," "tell me more about that" and "in what way," when a respondent gave an answer which was unclear. (Granger, Tr. 4174–75). Editing of the verbatim responses was done anytime the respondents did not respond to the questions. (Granger, Tr. 4175).

202. Two important quality control techniques were used in the tests. First, there is a technique department in Cincinnati that is responsible for a study as it is going on. If there are any problems in the local field office, the manager is [59] instructed to call the technique department to get it resolved (Granger, Tr. 4182–83). Once a problem is decided by the technique department, all other field supervisors are alerted to the decision. Second, completed questionnaires are monitored by Burke's quality control department to check whether the interviews are being conducted in the standard format (Granger, Tr. 4183–84).

203. All interviewers are Burke employees and are trained by Burke. This is to ensure that the manner of conducting interviews is standardized and of uniform quality. The interviewers are trained on the basic techniques of interviewing and are given some basic marketing research information and special techniques they will be called upon to use in their interviewing (Granger, Tr. 4170).

204. Part of the interviewer training consists of several days of actual practice conducting interviews among themselves and on the telephone. During the interview, interviewers are supervised by the office manager of a particular Burke office or another individual who is designated as job supervisor for that particular test (Granger, Tr. 4171).

205. Though the related recall score is a measure of the memorabili-

ty of the commercial, the verbatim responses are a better measure of the meaning of the ad than the related recall scores (Granger, Tr. 4222).

206. The copy tests in evidence by ASI and Burke were performed in a standard and reliable fashion. These tests or tests substantially identical to them were and are relied upon by large numbers of businesses, including manufacturers of OTC internal analgesics, for purposes of making normal business decisions. The Burke and ASI copy tests in evidence are reliable and probative evidence of consumer recall of advertising content for ads challenged in this proceeding.

3. CX 520—The Zeisel Copy Tests

207. Pursuant to a contract with the Federal Trade Commission, Dr. Hans Zeisel was responsible for the execution of three copy tests on three Bayer Aspirin advertisements—one print advertisement, CX 157, and two TV commercials, CX 52 ("Lee Trevino") and CX 75 ("Truisms"). The data from these surveys was analyzed by Dr. Zeisel and the resulting report is CX 520 (March, 1977) "The Consumer's Understanding of Three Bayer Advertisements."

208. The purpose of CX 520 was to determine the message conveyed to consumers by the two Bayer television commercials [**60**] and one print advertisement. These advertisements had been widely distributed through the media (CX 603E, H, U, V). Specifically, the study attempted to determine to what extent these advertisements were perceived as promising superior effectiveness of Bayer aspirin (CX 520B).

209. Dr. Zeisel was the principal author of CX 520. He was involved in the design of the study, the design of the questionnaire, the design of the samples, the examination of the samples size, and drafting of the final report (Zeisel, Tr. 4651). The Gallup Organization and Dr. Irving Crespi, then of Gallup, participated in the design of the questionnaire and did the field work for the print advertisement portion of CX 520 (Crespi, Tr. 4316–17). Response Analysis Corporation and Dr. Herbert Abelson participated in the design of the questionnaire and did the fieldwork for the TV advertisement portion of CX 520 (Abelson, Tr. 4520–21).

210. The three Bayer commercials selected were thought by Dr. Zeisel to be typical of Bayer commercials in general and were ones on which a substantial part of Blue Book funds were spent (Tr. 4655).

211. The print advertisement (CX 157) was shown to a probability sample of the U.S. population 18 years and over. The television advertisements (CX 52 and CX 75) were shown to a nonprobability sample consisting of persons 18 years and over in a variety of cities and walks of life (CX 520J).

212. After the advertisement was shown to the respondents, each respondent was asked a sequence of questions about the advertisement with successively narrowing focus. In the first questions, the respondent was asked what was the main point or points of the advertisements. Next, the respondent was asked what the advertisement said about Bayer aspirin as compared to other brands of aspirin. The next focus was even narrower, as the salient claim of the particular advertisement was quoted to the respondent, who was then asked what does the advertisement mean by that claim. Finally, each respondent was asked to answer the most narrowly focused question: "Does the advertisement suggest or does it not suggest that Bayer is more effective in relieving pain than any other brand of aspirin?" The questions were asked in this order of successively narrowing focus so that the consumers' answers to the earlier question would not be tainted by knowing in advance the content of the subsequent narrower questions (CX 520J–K).

213. Dr. Crespi reviewed the print questionnaire (CX 520Z008–Z012) to CX 520 and presented it to determine whether it conformed to good professional practices. The pretest indicated to Dr. Crespi that no major changes were required (Crespi, Tr. 4316–17). **[61]**

214. Dr. Abelson reviewed the TV questionnaire (CX 520Z014–Z024) to CX 520 and pretested them. A total of four pretests were carried out by Responses Analysis (Abelson, Tr. 4528). The initial pretest identified that the early drafts of the questionnaires were, in fact, leading some of the respondents. He testified that through the process of redrafting and pretesting, these problems were eliminated and the final questionnaire design was not leading and conformed to good professional practice (Abelson, Tr. 4530–4542).

215. Dr. Ivan Ross, (CPF 12) acknowledged the acceptability of the questionnaire design in CX 520 and identified it as a "funneling approach" (Ross, Tr. 5770–01). A funneling approach refers to a set of questions moving from an unaided form to a progressively and more aided form (Ross, Tr. 5771). Dr. Ross uses such a procedure for most of the copy tests that he conducts (Ross, Tr. 5771–72). The funneling technique is fairly standard in copy test research of consumer interpretations of advertisements (Crespi, Tr. 4322; Ross, Tr. 5771–72).

216. Dr. Crespi analyzed the questionnaire for CX 520 to satisfy himself that the questions were understandable and not confusing, were answerable in the terms in which they were formulated, were not biased or leading, produced data about the issue being investigated, and were physically and psychologically administratable. In approving the questionnaire, Dr. Crespi felt that these concerns had been adequately addressed for CX 520 (Crespi, Tr. 4317–18).

217. The respondents to CX 520 who were asked about CX 157, a

Bayer print advertisement, were selected on a national probability basis. The respondents were interviewed personally in their home by field representatives of the Gallup Organization. Respondents were selected from a sample drawing from Gallup's master national probability sample of interviewing areas. This sample is based upon the latest data available from the Census Bureau. The country is divided up into blocks or clusters of blocks by a standard method, various blocks of clusters were selected for use in this study. Within a block or cluster, a starting point was selected by Gallup in a random manner. Gallup interviewers were then given a map of the area to which they were assigned and this randomly starting point was indicated on the map. The interviewers were instructed to conduct an interview at each of the households. Then using a randomized procedure they selected one of the individuals in the household to be interviewed. If that selected individual was not at home, the interviewer was to make a call back to attempt to complete the interview in that household. Up to four calls were made in each household. No substitution of households were permitted (Crespi, Tr. 4326–28). **[62]**

218. Once the Gallup interviewers were granted access to a respondent's home, the Gallup interviewer read the text of CX 157 to the selected respondent. Next the respondent was handed the advertisement and allowed to read it. After the respondent had finished looking at the advertisement, the Gallup interviewer took CX 157 back and did not show it again to the respondent. Next, the interviewer asked the respondent the questions set forth in CPF 106, recording the answer fully in the respondents' own words (CX 520Z009). The interviewers did not summarize or paraphrase the respondents' answers (Crespi, Tr. 4331–32). The response rate to the print portion of CX 520 was about 60%.

219. Through the process of validation, Gallup took steps to be certain that the interviewers actually conducted the designated interviews. Gallup validated one-third of the interviews and the validation revealed no problems (Crespi, Tr. 4334, 4350).

220. When Gallup received the final and completed questionnaire from the fieldworkers, personnel at Gallup went through a standard quality control procedure to verify the interviews had been conducted in accordance with the instructions. Gallup then sent the completed and filled out questionnaires to Ilsa Zeisel for coding (Crespi, Tr. 4337).

221. The answers to the print portion of the results of CX 520 were statistically weighted according to demographic characteristics. The standard Gallup weighting procedure was used to adjust the data for any slight over or under representations of the population. This procedure is based upon a system that is used by the Census Bureau in its

monthly population surveys and by many other large survey organizations. The result of this weighting is to bring the final calculations as close as possible to the true population characteristics (Crespi, Tr. 4339). According to Dr. Crespi, although some of the questionnaires were not weighted, the impact of such missing weights was minimal on the final results to CX 520. The effect of the missing weights would have had, at most, about a one percentage point impact on the final results (Crespi, Tr. 4365–71).

222. Respondents to the TV portion of CX 520 were shown two 30-second commercials, one control commercial followed by a Bayer Aspirin commercial. After the commercials were run, the respondents filled out a self-administered questionnaire (Abelson, Tr. 4555–47; CX 520Z045–Z051).

223. Data were collected from 240 respondents from nine separate groups. Group interviews were held in the areas Springfield, Massachusetts; Kansas City, Missouri; Atlanta, Georgia; and Providence, Rhode Island. **[63]**

224. The first commercial was the same for all nine groups—an advertisement for Scott Super Turf Builder. The second commercial alternated between two Bayer Aspirin commercials—the Trevino commercial (CX 52) and the Truisms commercial (CX 75). Four of the groups (92 respondents) saw the Trevino commercial and five of the groups (148 respondents) saw the Truisms commercial (Abelson, Tr. 4552–53; CX 520P).

225. The community groups from which the TV samples were recruited consisted, for the Trevino survey, of four groups—YWCA members and friends, Methodist Church members, Toastmasters' Club, and Catholic Women's Club; for the Truisms survey, a Golden Age group, PTA members, Black community group, community social club, and Rotary Club members (RX 306, RX 307).

226. The group approach was used because this is an economical way of getting data and groups to provide a way of getting diversity and variations in the characteristics of the people who were exposed to the copy test (Abelson, Tr. 4547).

227. Respondent disputes that the nonprobability group approach was necessary on cost grounds, noting that Dr. Lipstein has recently completed a national probability survey of consumer perceptions of a TV commercial in the context of other litigation (Lipstein, Tr. 11970).

228. The completed questionnaires from both the print portion and the TV portion of CX 520 were sent by the Gallup Organization and Response Analysis to Ilsa Zeisel for coding. Ilsa Zeisel coded the verbatim responses from the original questionnaires pursuant to the instructions of Dr. Zeisel (Zeisel, Tr. 4686).

229. Dr. Hans Zeisel established the coding scheme for the re-

sponses to CX 520 (Zeisel, Tr. 4679–81). For the purpose of tabulations, the respondent answers to the questions asked in CX 520 were classified and coded according to the system established by Dr. Zeisel. He established seven categories into which a consumer response might fall.

230. The first category included all consumers who perceived the advertisement as claiming that Bayer is the best aspirin by an explicit reference to Bayer superior effectiveness. The second category was comprised of all consumers who stated the advertisement's message to be that Bayer is superior to other aspirins with respect to effectiveness but these consumers did not explicitly state whether the superiority pertains to all other aspirins or to only some. The third category included all consumers who stated the message in terms of Bayer's effectiveness without referring to its competitive position. Categories 4, 5, and 6 followed the patterns of the first three categories except that the answers do not contain an explicit reference to Bayer's [64] effectiveness. The seventh category included all other answers. When a consumer gave more than one response to a question, he was classified according to his most explicit answer (CX 520M–0; Zeisel, Tr. 4680–82).

231. Appendix VIII of CX 520 (CX 520Z005–Z068) sets out the many codes used by Ilsa Zeisel. It also identifies how each code was classified into one of the seven categories established by Dr. Hans Zeisel, as set forth in CPF 122 (CX 520N).

232. The results of the coding, pursuant to the instructions and scheme established by Dr. Hans Zeisel, are set forth in Tables 1, 2, 3, 4, 5, and 6 of CX 520. Tables A–E of CX 520 contain cross tabulation of the data contained in CX 520 according to demographic characteristics.

233. To supplement the specific coding by Ilsa Zeisel, Dr. Hans Zeisel went through and read each questionnaire to determine whether the respondent perceived that the message of the advertisement was that Bayer is therapeutically superior to other aspirin. The results of Dr. Zeisel's analysis of the verbatims are reported in CX 520 at page Y (Zeisel, Tr. 4696–99).

234. Respondent is critical of many aspects of CX 520 and its experts note deficiencies in the selection of samples used in the surveys, the absence of a benchmark or control survey, the design of the actual questionnaire, and the coding classification and data analysis.

235. Dr. Zeisel has conceded that the TV survey samples are not probability samples. As a consequence, the samples cannot be considered representative of the universe and projectable to it. In addition, it is not possible to calculate an error with a measurable statistical degree of confidence. These are the two attributes of a nonprobability

sample. (Crespi, Tr. 4359–60; Zeisel, Tr. 4674, 4789–90; *see* Amstutz, Tr. 9999; Lipstein, Tr. 12012–13)

236. Dr. Lipstein, respondent's expert, testified that use of such samples did not meet current professional standards or practice (Lipstein, Tr. 11963, 11973–74), and that it is not proper to rely on the results of a study using such sampling to arrive at a judgment of the perceptions or attitudes or behaviors of consumers in general (Lipstein, Tr. 11968).[5] **[65]**

237. Dr. Zeisel has recognized the limited application of this portion of his work. He stated with respect to the nonprobability samples in this case that "the best we can do with it is to claim that we will describe these people . . . demographically, as well as we can. Here is what these 300, I think there were 300 people, would say about it. That was all. There was no claim about general statements." (Zeisel, Tr. 4790, 4792). He also admitted that the averaging of data from the three copy test surveys is inappropriate (Zeisel, Tr. 4685).

238. Respondent's witness Cortesi undertook a demographic analysis of the TV survey samples according to age, education, income and sex, using data on the computer tapes supplied by the FTC (Cortesi, Tr. 9832, 9876–77). This is presented in RX 141(a), "Analysis of the Use of Combined Data TV Ad and Print Ad Surveys in the Zeisel Advertising Study, CX–520," pages E–O (Amstutz, Tr. 10002; Cortesi, Tr. 9832–34).

239. In this analysis, respondent's experts compared the demographics of the probability sample used for the print advertisement survey, of a second probability sample (also done by Gallup) for the image study, CX 521, and of the non-probability samples used for the TV ad surveys. The comparison was on the same demographic dimensions used by Dr. Zeisel—age, education, income and sex (adjusting the demographic breaks for comparability) (Cortesi, Tr. 9834–35). The results are presented in RX 141(a) E–O, Tables A–1 to A–4, B–1, B–2.

240. The results show that two probability samples—for the print advertisement survey in CX 520 and the image study in CX 521—were very similar, and the data show very high to high probability that they were drawn from the same population (Amstutz, Tr. 10004; RX 141(a) M, N, Tables C–1, C–2).

241. In contrast, the Trevino and Truisms samples differed from one another, each differed from the print advertisement probability sample, and these differences are statistically significant at a high confidence level (Amstutz, Tr. 10005–06; Cortesi, Tr. 9838–39; RX 141(a) M, N).

[5] However, Dr. Lipstein could only recall one occasion when he had used a national probability sample in a copy test (Lipstein, Tr. 12074), and Dr. Lipstein himself acknowledged that national probability samples are not necessary for measuring possible consumer interpretations of advertising copy (Lipstein, Tr. 12059).

242. The TV samples differed significantly from the print advertisement survey sample in every demographic variable with a p-value of less than .05 to less than .001, so that there is no **[66]** chance that the TV samples were representative (RX–141(a) L–O; Amstutz, Tr. 10010–11). There is no chance that the Trevino sample came from the same population as the print sample on the dimensions of education, income and sex; for age, there was a 4% chance. There is no chance that the Truisms sample came from the same population as the print sample in terms of age, education or income. On sex, there was a small chance. The minimum confidence that can be applied to the assertion that the TV survey populations are different from the print ad probability population would be 96.1% for Trevino and 97.8% for Truisms (Amstutz, Tr. 10004–06).

243. The Trevino and Truisms samples were not similar. The differences between the two samples were statistically significant in two of the four demographic variables. In comparing the Trevino and Truisms samples, there is no basis for asserting that they are equivalent on age or sex; there is a low basis for asserting that they are similar on education and income (Amstutz, Tr. 10006; Cortesi, Tr. 9839).

244. The instructions given to Gallup interviewers conducting the print survey explicitly stated that only questions as written on the questionnaire were to be asked. There must be no explaining of questions in the interviewer's own words. Interviewers were cautioned not to ask probing questions since the series of prescribed questions were regarded as the only permitted probes (CX 520Z043). However, review of the print survey questionnaires by respondent's expert Cortesi disclosed that a number of the questionnaires contained notations such as (P) or (X) which is the usual shorthand for a probe. Eighty-eight questionnaires, or 12% of the sample, contained such notations (Cortesi, Tr. 9828–29).

245. Complaint counsel's witness, Dr. Crespi, testified that the parenthetical indications on the questionnaires probably designate the instances when the interviewer repeated one of the questions. It is a standard practice (and stated in the Gallup interviewer's manual) to repeat a question when a respondent indicates an inability to answer the question (Crespi, Tr. 4402–04). He believed it would be inappropriate to eliminate such questionnaires from the data base (Crespi, Tr. 4404).

246. Several of respondent's expert witnesses attested to the principle that the proper procedure is to eliminate a questionnaire and not include it in the resulting data if it is found that an interviewer had used improper or unauthorized probes. Among complaint counsel's witnesses, this was stated to be the practice of the Burke organization

by the official testifying for complaint counsel (Granger, Tr. 4217; RPF 5.167). It was agreed to by Dr. Crespi of the Gallup Organization as a proper principle (Crespi, Tr. 4400). [**67**]

247. It was also Dr. Lipstein's judgment that when interviewers violate instructions in gathering data, the questionnaires evidencing violations of instructions must be discarded. Dr. Lipstein described his experience in discarding survey questionnaires containing such interviewer errors in a survey where the cost of the interview was very high, citing the high standards required for litigation purposes (Lipstein, Tr. 11975–76).

248. Dr. Zeisel acknowledged that if there was a probe in the first two questions, then the respondents could not be properly classified as reporting Bayer therapeutic effectiveness for purposes of his Table 1 in CX 520, which was intended to cover only the answers to the first two prescribed questions without further probing (Zeisel, Tr. 4978–79).

249. The effect of eliminating the disputed questionnaires would be to reduce the response rate. The response rate in the print survey was stated by the Gallup witness, Dr. Crespi, to be about 60% (Crespi, Tr. 4335). Zero weightings had reduced the response rate to about 59% (Crespi, Tr. 4362–63); Cortesi, Tr. 9834; Zeisel, Tr. 4708–10). Dr. Crespi regarded that 60% was in conformity with generally accepted standards for personal interview surveys of individuals in a national sample (Crespi, Tr. 4335). He acknowledged that below 50%, no projections were possible and a survey at such low completion rate should have studied the nonrespondents or undertaken other procedures (Crespi, Tr. 4419–20, 4422–23). Mr. Cortesi regarded the standard for consumer surveys using probability samples done door-to-door to be a 75% response rate (Cortesi, Tr. 9831). If the questionnaires with unauthorized and unidentified probes were eliminated, the sample would be reduced to below what is considered acceptable (Amstutz, Tr. 9999–10000, 10018; Cortesi, Tr. 9831).

250. Respondent argues that a benchmark could have been developed by use of a reference advertisement, a neutral or unchallenged advertisement, and showing the control advertisement and the test advertisement to comparable groups. The resulting statements by respondents about the control advertisement would be compared to the statements reporting perceptions of the test or challenged advertisement, and the difference could be attributed to the representations in the test or challenged advertisement (Amstutz, Tr. 10023, 10025; Lipstein, Tr. 11960–61, 12219).

251. Another approach would be to use a before and after mechanism in which respondent gives perceptions of products before seeing

an advertisement and after seeing an advertisement, to measure the impact of the advertisement (Amstutz, Tr. 10023).

252. But, as noted by complaint counsel, it was not Dr. Lipstein's testimony that a control ad was necessary to meet [68] acceptable survey designs. This is less serious than some of respondent's other criticisms of CX 520.

253. The survey questionnaires were administered in a way that greatly increased the attention and recall of respondents. Thus, in the TV surveys, respondents were instructed that they would see films and be questioned thereafter (CX 520Z014). This is not the kind of situation normally experienced at home. It substantially increased the level of recall of advertising claims compared to a real-life situation (Miles, Tr. 9334; Lipstein, Tr. 11977, 11980).

254. Dr. Zeisel acknowledged that a good copy test simulates as closely as possible a real-life situation. He further acknowledged that the copy tests in CX 520 were artificial in that one does not normally review an advertisement with the expectation of being questioned about it, and that directing the consumers' attention to an advertisement results in a heightened tension focus and awareness of it (Zeisel, Tr. 4777–4778). Thus, in comparison to a Burke survey, you would expect a higher level of response from the method used by Dr. Zeisel; 100% of the respondents should have remembered the advertisements as compared to about 20% in a Burke (Zeisel, Tr. 4780–82).

255. In the print survey, the series of questions to be asked (and recorded) by the interviewer was:

1. What would you say is the main point of this advertisement?
2. Does the advertisement make any other points? What are they?
3. What does the advertisement say about Bayer aspirin as compared with other brands of aspirin?
4. What else does the advertisement say about Bayer as compared to other brands of aspirin?
5. The advertisement said that "Bayer makes a better quality aspirin." What does the advertisement mean by "better quality?"

(CX 520Z009)

256. In the TV surveys, the series of questions, to be answered by respondents, was:

1. Thinking just of the aspirin commercial, what would you say was the message of this commercial? [69]
2. What were the other messages in this aspirin commercial?
3. What did the commercial say about Bayer aspirin as compared with other brands of aspirin?
4. For Trevino - The commercial said that "Bayer is the best aspirin." What does the commercial mean by that? In what way or ways is Bayer the best aspirin?

5. For Truisms - The commercial said that no other leading brand of aspirin could match Bayer's overall high standards. What does the commercial mean by that?

(CX 520Z016-Z019)

257. I have relied on only the responses to the first two questions (Questions 1 and 2 in print survey, Questions 2 and 3 in TV surveys) as a basis for ascertaining the message conveyed by the tested advertisements.

258. Respondent concedes that the first question in the surveys was unobjectionable, a fair, open, free-response question (Miles, Tr. 9334, Cortesi, Tr. 9810). Dr. Lipstein was critical of the first question because it implied that there was a particular message in the commercial. In his view, a question such as "Tell me everything you remember about the commercial" is preferable (Lipstein, Tr. 11978). The classic survey approach is to provide as little structure as possible because, each time a question is asked, information is given (Lipstein, Tr. 11977).

259. The second question in the print survey was a reasonable probe—Does the advertisement make any other points? What are they? (Cortesi, Tr. 9810; Miles, Tr. 9343). However, the probe in the TV questionnaires was criticized. It was in the form—"What were the other messages in this aspirin commercial?" This is unacceptable because it tells respondents that there must be other messages, and forces them to come up with points in addition to those already given (Miles, Tr. 9335; Cortesi, Tr. 9818–19; Lipstein, Tr. 11978).

260. Dr. Crespi stated that Question 2 in that survey was probably worded "Does the advertisement make any other points? What are they?" to avoid telling the respondents that there were other points, but simply to let them decide and then respond. This was in contrast to asking what other points does the advertisement make (Crespi, Tr. 4407). The probe in the TV survey did in fact ask what other messages there were, and is subject to criticism on that ground.

261. Respondents' witnesses find the subsequent questions to be unacceptable, and their arguments are persuasive. The **[70]** next question or questions (Questions 3 and 4 in the print survey, Question 4 in the TV surveys) tell respondents that a comparison was made and further that the comparison was between Bayer and other brands of aspirin, all of which was information which the respondent may not have noticed. Further, this question would lead respondents to guess what Bayer would be likely to say versus other brands of aspirin, and invited respondents to come up with puffery statements of being better, common to advertising. This was highly suggestive and improper, leading to forced responses (Miles, Tr. 9336; Cortesi, Tr. 9810–12; Lipstein, Tr. 11979). Dr. Zeisel acknowledged that the questionnaire

could have asked whether the commercial said anything about Bayer versus other aspirin and then inquired what does it say. This was the form of one of the earlier drafts of the questionnaire (Zeisel, Tr. 4922–23).

262. The next question (Question 5 in print and TV surveys) took a quotation from the advertisement and forced respondents to focus upon it whether or not they had perceived or remembered it. The statements taken from the advertisements were out of context, and respondents were required to speculate.

263. The first draft of the TV survey questionnaire contained the question, "Did the commercial say anything about Bayer Aspirin being the best aspirin?" with followups. According to Dr. Abelson of Response Analysis Corp., the purpose of this formulation was to avoid telling the respondents what the commercial said, and to minimize any cue or suggestion from the question (Abelson, Tr. 4580–81). Question 5 in the surveys, as eventually used, did not avoid that risk but in fact forced respondents to respond to what the question told respondents about them.

264. The above questions were followed in all the surveys by Question 6, a direct question asking respondents whether the advertisement "suggested" that Bayer was more effective in relieving pain than any other brand of aspirin and requiring them to answer yes, no or not sure (CX 520Z010, Z020). Question 6 was not justified by the need to determine whether "inarticulate" respondents got the alleged therapeutic message, as argued by Dr. Zeisel (Zeisel, Tr. 4665).

265. In the CX 520 survey, after obtaining the TV survey data, Response Analysis developed a full coding system to cover the range of responses received in the survey and submitted tabulations and analyses in terms of a full range of response categories (Abelson, Tr. 4611–15; RX–308).

266. This Response Analysis Corp. report was submitted to Dr. Zeisel. Dr. Zeisel redid the coding and classification of the verbatim responses. He told Dr. Abelson that Response Analysis codes were not specific enough and that more information could be gleaned from the open-ended comments (Abelson, Tr. 4524–25, 4575–76). [71]

267. Under instruction from Dr. Zeisel, the responses to the three copy tests in CX 520 were coded by his sister, Ilse Zeisel, into a large number of codes. Dr. Zeisel personally assigned the codes to the following seven classifications:

1. Bayer is best with explicit reference to effectiveness;

2. Bayer is better than other aspirins with explicit reference to effectiveness;

3. Bayer is praised without explicit comparisons to other aspirins with explicit reference to effectiveness;

4. Bayer is best without explicit reference to effectiveness;

5. Bayer is better than other aspirins without explicit reference to effectiveness;

6. Bayer is praised without explicit comparisons to other aspirins without explicit reference to effectiveness;

7. All other aspirins.

(Zeisel, Tr. 4681; CX 520L–N)

268. Dr. Zeisel focused attention on the sum of categories 1 and 2 as reflecting respondents who were classified as reporting Bayer superior effectiveness according to his coding and classification system. These two categories did not include comparative pharmaceutical and manufacturing quality responses (Zeisel, Tr. 4682; CX 520; Z056–57; Z061–Z062).

269. Respondent has argued that the inadequacy of Dr. Zeisel's approach was made apparent by the fact that the miscellaneous category "all other comments" was abnormally large, including an unduly large percentage of respondents, in Table 1, 29 to 62% of respondents (CX 520P) (Cortesi, Tr. 9785–86; Miles, Tr. 9348; Lipstein, Tr. 11996). This violates professional standards (RPF 5.308–5.311). In addition, although these advertisements were about quality, Dr. Zeisel failed to have any classification for quality (Miles, Tr. 9348). Mr. Cortesi also noted that CX 520 presented an "average of all surveys", combining results from three different copy tests, which is not normal or accepted practice (Cortesi, Tr. 9785–86). Dr. Zeisel later in his testimony sought to withdraw the latter data (RPF 5.251).

270. CX 520V, Table 4, sets forth what Dr. Zeisel called "The Message Conveyed by the Bayer Advertisements as Reflected by the Consolidated Free Answers." This purported to [72] "consolidate" the results of all the verbal responses to Questions 1–5 in the print survey, Questions 2–5 in the TV survey. According to CX 520, the "consolidation" of the answers was accomplished by classifying each respondent by "the most explicit answer" in those responses (Zeisel, Tr. 4688; CX 520 U).

271. In the course of his study, Dr. Zeisel made a number of changes in coding and general conception. The coding structure was changed, as evidenced in the difference between the code structure on the tapes and the final format. In addition, the report itself, CX 520, went through three revisions. There was an initial document in May 1976, an August 1976 revision, and a March 1977 revision. These required changes in the data on the computer tapes because Dr. Zeisel changed

certain codes and categories in which responses were classified (Cortesi, Tr. 9805, 9807–09).

272. On February 14, 1977, by letter to respondent's counsel, Dr. Zeisel made a number of changes in coding of specific responses from the earlier version of his report. In addition, Dr. Zeisel stated that he had reread all the questionnaires and undertaken to classify respondents based upon his reading of their questionnaires as a whole, apart from the coding and classification system previously used addressed to specific responses (Zeisel, Tr. 4835–39; RX 314). Based upon such classification of questionnaires as a whole, Dr. Zeisel added Table 4A and Table 6A to CX 520. Table 4A classified all respondents either into his category 1 or 2, or "All Other Responses" based upon reading questionnaires as a whole. Table 6A correlated such classifications with the respondent's answer to the direct Question 6 (CX 520Y, Z006; RX 314).

273. In his testimony in this case, Dr. Zeisel acknowledged that the changes referred to in his letter of February 14, 1977, which made coding changes, and which made category changes from reading the questionnaires as a whole, were in the direction of increasing the number of respondents who reported Bayer's superior effectiveness (Zeisel, Tr. 4837). He acknowledged that, before doing the surveys in this case, he had never before read through all the questionnaires in a survey to make a decision about their classification and the results of the survey (Zeisel, Tr. 4834).

274. In his testimony, Dr. Zeisel stated that he relied upon his reading of the CX 520 questionnaires as a whole, and proposed that the Commission should give it the "greatest weight." Tables 4A and 6A resulting from his reading were, he said, "crucial." They were the "final tables." the "final analysis," they "superseded" the tables produced by his coding and classification system (Tables 4 and 6) and should be the focus of attention (Zeisel, Tr. 4699, 4703, 4712, 4847, 4901).

275. In cross-examination, Dr. Zeisel refused to be bound by the listing in his letter of February 14, 1977, of specific [**73**] answers in the questionnaires which were the basis for his reclassification of certain respondents by the coding and classification system. Dr. Zeisel stated that the letter was an error, and he would only consider the classification of respondents by looking at all the responses in the questionnaire taken as a whole (Zeisel, Tr. 4842, 4849, 4995, 4998).

276. Dr. Zeisel explained that in his reading of the questionnaires as a whole for purposes of Tables 4A and 6A, he classified respondents by combining the responses to various questions. Thus, he combined a statement in response to one question reflecting Bayer's superiority *without* reference to effectiveness, *e.g.*, Bayer is best, with a statement

in response to an entirely separate question reflecting Bayer's efficacy *without* any comparative, *e.g.,* Bayer is effective. His position was that one statement referred to or explained the other regardless of which came first, regardless of the number of intervening statements and regardless of the absence of any stated or indicated connection between them (Zeisel, Tr. 4845, 4850–51, 4870, 4943–44, 4957, 5001–02, 5007–08).

277. A number of respondents were classified as reporting Bayer's therapeutic effectiveness by Zeisel and they inconsistently did not answer "Yes" to the direct question, whether the advertisements suggested that Bayer was superior in effectiveness to other aspirin. This involved 7% of the Trevino respondents, 9% of the Truisms respondents (compare CX 520Y, Z006).

278. A number of specific errors of classification of questionnaires and coding of responses by Dr. Zeisel were brought out during the hearing.

279. Dr. Zeisel stated that one questionnaire in the Trevino survey, No. 14204, should be eliminated from the list of those classified as reporting Bayer superior effectiveness in Table 4A. There was no way to establish that the respondent believed the commercial indicated Bayer's superiority to other aspirins, because the statement "it is fast at killing pain, it's good for headaches," was not comparative (Zeisel, Tr. 4775).

280. On cross-examination, Dr. Zeisel acknowledged error in classifying another questionnaire in the Trevino survey, No. 12221, in the group reporting Bayer therapeutic superiority. This was an error because the answers to Questions 2 and 3 did not specifically refer to Bayer, and so was incorrectly classified for purposes of Table 1 and Tables 4A and 6A (Zeisel, Tr. 5011–12). Dr. Zeisel acknowledged that the commercial had two messages, aspirin vs. other pain relievers and Bayer vs. other aspirins. It is not possible to tell from the response "Works best" what the respondent was referring to (Zeisel, Tr. 5012). **[74]**

281. Dr. Zeisel made a similar acknowledgment with respect to the use of the word "it" or "they" in the responses to the first questions of another questionnaire in the Trevino survey, No. 11312, which stated "That they have better result" and "It is the leading brand of other headache products." This would be a dubious classification for purposes of CX 520, Table 1, because the language could refer to the aspirin group rather than Bayer (Zeisel, Tr. 5013–14; *see also* 4921).

282. Similarly, Dr. Abelson agreed that the answer to the first question in another questionnaire in the Trevino survey (No. 14215) was addressed to the part of the commercial dealing with straight aspirin vs. other pain relievers and indicated that it was that message

that registered with the respondent. This was also probably true of the response to Question 3. It is possible that, without the cue about Bayer in the following questions, this respondent would have played back only responses that had to do with aspirin vs. other pain relievers (Abelson, Tr. 4606–07, *see also* questionnaires discussed at Tr. 4608).

283. Dr. Abelson also acknowledged, with reference to a questionnaire in the Truisms survey, which referred to a benefit for "colds" in response to the first question (No. 2110), that the respondent could have been talking about the general product category, since the question did not specifically refer to Bayer Aspirin, the answer did not contain any mention of Bayer, and there was nothing in the advertisement that made reference to colds (Abelson, Tr. 4586–87).

284. Dr. Zeisel classified a number of respondents as reporting Bayer's therapeutic superiority because of the term "best pain reliever." He would not have so classified them if the answer had been "best analgesic" and did not so classify "best aspirin" (Zeisel, Tr. 4878, 4887). On cross-examination, Dr. Zeisel reluctantly agreed that "pain reliever" could refer to a product category (Zeisel, Tr. 4879, 4937–38). It was a reasonable inference that "best pain reliever" could be often used as meaning "best analgesic" as a product category without referring to specific benefits (Zeisel, Tr. 4937–38).

285. Dr. Zeisel later went further and discussed the impact of removing from Table 4A those so classified because of the use of the term "best pain reliever." He made certain computations with respect to the effect this would have upon the TV ad survey results; he had not had time to undertake the same review for the print ad survey (Zeisel, Tr. 5028, 5033).

286. Dr. Zeisel acknowledged that safety or freedom from side-effects may properly be considered as separate and distinct from effectiveness in relieving pain. On that basis, those questionnaires which he had classified as reporting Bayer's superior effectiveness because of statements relating to safety would be subtracted from the classification (Zeisel, Tr. 4816–17, 4871, 4960). **[75]**

287. There were 16 or 17 questionnaires in the Truisms survey in which handwritten changes were made on Question 5 by the person administering the survey to a Golden Age group. If Dr. Abelson of Response Analysis had discovered these handwritten changes at the time the questionnaires were received, he would have eliminated the questionnaires from the survey (Abelson, Tr. 4592). They should be eliminated from the Truisms survey.

288. There are two questionnaires in the Truisms survey which appear to be identical—with similar misspellings, almost identical responses and similar handwriting; if the correspondence between

these two questionnaires had been noted when they came back, a judgment would have been made about whether to eliminate them (Abelson, Tr. 4593–94). These should be eliminated from the Truisms survey.

289. In connection with one questionnaire in the print survey (No. 377), Dr. Zeisel stated that the answer did not indicate "best," but rather one of the best. He stated that it was good enough that Bayer be better than some to be classified as a report of Bayer's therapeutic superiority, and also indicated that this was a "marginal case." (Zeisel, Tr. 4945–46).

290. Even assuming that these questionnaires were inappropriately classified, the impact of their removal from the 757 responses to CX 520, (CX 520P) is serious, but does not totally negate Dr. Zeisel's findings.

291. Dr. Lipstein testified that established professional standards dictate that the person who organizes and conducts a study, especially for litigation purposes, should not do the coding of the study to avoid bias or interaction of the experimenter with the experiment (Lipstein, Tr. 12214).

292. While this might be a preferred practice, it appears that various surveyers have different policies on this aspect (Crespi, Tr. 4394, 4398; Zeisel, Tr. 5022–23).

B. *A Number of Sterling Advertisements Made the Challenged Representations*

1. Complaint Paragraph 10(A)

293. Sterling represented, directly or by implication, that Bayer Aspirin is superior in terms of significant therapeutic effect to any other plain 5-grain aspirin. This representation was made in the following advertisements: CX 13, 15, 19, 37–39, 47, 48, 50–52, 54, 56–58, 60–67, 69, 70, 72, 74, 79, 99, 101–104, 109, 117, 122–129, 145–147, 150, 152, 155–158, 161.

294. The advertisements listed in F. 293 contain one or both of the two following claims: **[76]**

(a) That Bayer Aspirin is faster acting and/or gentler aspirin than any other aspirin (*e.g.,* CX 47, 48, 51, 79, 99, 109, 155–158, 161); and

(b) That Bayer Aspirin is the best pain reliever or the best aspirin (*e.g.,* CX 13, 15, 19, 37–39, 48, 50, 52, 54, 56–58, 60–67, 69, 70, 72, 74, 101–104, 122, 123, 126).

295. For example, CX 51 (CX 51a is a film) is a 1971 Bayer television commercial (30 seconds) entitled "Alike." Although the commercial begins by suggesting that all USP aspirin is not the same quality because Bayer surpasses USP standards "in many ways," a good half

of this short commercial is devoted, while the announcer is holding up the Bayer bottle, to the statement:

For example, Bayer standards require complete tablet disintegration within thirty seconds. That's ten times faster than the accepted five-minute standard. It's one of the things that help make Bayer fast and gentle.

Viewing the commercial as a whole, the representation that Bayer Aspirin is faster and more gentle than other aspirins and is therapeutically superior to other aspirins is clear and unequivocal.

296. CX 99, a 30-second commercial entitled "Bayer Man—Bill Joyce" uses identical language and appears to be a radio version of CX 51.

297. To cite a few more examples, CX 48 is the storyboard of a 1972 television commercial (60 seconds) entitled "Ozzie Nelson." Although the main message of this commercial is that all aspirin is not alike and plain aspirin is preferred to combination products, the advertisement also suggests that a "new study" found Bayer Aspirin to have "superior" "speed of disintegration," among others. Some consumers may reasonably perceive this commercial as representing also that Bayer is a faster-acting aspirin and therapeutically superior to other aspirins.

298. Although CX 48 mentions "speed of disintegration" only in passing (as compared with CX 51 which dwells on that theme), CX 48 suggests Bayer is therapeutically superior to other aspirins by also claiming "aspirin's the best pain reliever, and [77] Bayer is the best aspirin." The "best aspirin" claims in the context of the advertisement as a whole clearly suggests that Bayer is the best pain reliever and therapeutically superior to other aspirins.

299. CX 52 (52a) is a 1971 television commercial (60 seconds long) for Bayer Aspirin entitled "Lee Trevino." This was one of the two television commercials studied in the Zeisel Copy Tests (CX 520). The content of this advertisement is similar to CX 48 "Ozzie Nelson" discussed in F. 297 *supra,* except that CX 52 does not mention "speed of disintegration" while both CX 48 and CX 52 refer to "purity" and "freshness." However, CX 52 claims "Bayer makes the superior aspirin" and closes the commercial with the familiar tag line "aspirin is the best pain reliever and Bayer is the best aspirin." Many consumers may reasonably perceive the commercial as representing that Bayer Aspirin is therapeutically superior to other aspirins.

300. The Zeisel Copy Tests (CX 520) provide confirmatory evidence with respect to CX 52. Table 1 of the Zeisel Study shows that about 13% of the respondents (subject to a sampling error of $\pm 7\%$, assuming the sample were a probability sample which it was not) received

a superior "effectiveness" message for Bayer in response to open-ended questions 2 and 3 (CX 520F, P, Z37).

301. CX 157 is a print advertisement for Bayer Aspirin, which was copy tested in CX 520, the Zeisel Copy Tests. The main message of this advertisement is "Bayer makes a better quality aspirin," headlined in oversize prints. The small print body of the advertisement also says Bayer is "the finest quality aspirin you can buy." However, the small prints also refer to "speed of disintegration" and closes with the tag line "aspirin is the best pain reliever, and Bayer is the best aspirin." Many consumers may reasonably perceive CX 157 as representing that Bayer is a therapeutically superior aspirin.

302. The Zeisel Copy Tests (CX 520) provide confirmatory evidence with respect to CX 157. Table 1 shows that about 11% of the respondents (subject to a probability sampling error of $\pm$ 3%) played back "superior effectiveness" message for Bayer in response to open-ended questions 1 and 2 (CX 520D, p. Z37).

303. CX 13 (13a) is a 1967 television commercial (30 seconds) for Bayer Aspirin entitled "Epidemic Crawl." Although the main message of the commercial is that for the relief of symptoms of cold or flu, aspirin is a recommended remedy, the advertisement also claims that Bayer is "the world's best aspirin." The "best aspirin" claim is likely to be reasonably perceived by consumers as saying that Bayer is therapeutically superior to other aspirins.

304. CX 15 (15a) is a 1969 television commercial (30 seconds) for Bayer entitled "Foul Weather Friend." Although the [78] main message of the commercial is Bayer Aspirin is good for aches and pains "all year round," it also claims Bayer is "the best pain reliever." The phrase "the best pain reliever" clearly means "therapeutic superiority" to most consumers. CX 15 is thus a clear example of a representation of therapeutic superiority for Bayer Aspirin.

305. When an advertisement makes a claim of "best" for an aspirin (instead of "best quality"), the unqualified claim will be understood by consumers in the context of superior therapeutic efficacy. Because the advertisements in question are about a drug product which is taken primarily for the relief of pain, the use of unqualified comparatives (such as "superior," "better" or "best") will be perceived by consumers as claiming greater therapeutic effect, unless the comparative is expressly or unmistakably directed to some other attribute, such as quality ("superior quality," "better quality" or "best quality"). (CX 105, a 1972 radio commercial for Bayer discussed in F. 318, *infra,* is one example of an advertisement wherein each comparative is expressly and unmistakably coupled with "quality" throughout the commercial.)

306. "Puffery" or "puffing" is a recognized phenomenon in advertis-

ing and employs such superlatives as "the best," "the world's best," and other hyperbolic expressions. When recognized by consumers as such, puffing is discounted by them. Consumers know by common sense and daily experience that puffing is not meant to be taken seriously (Zeisel, Tr. 4896; Haley, Tr. 10569).

307. Whether consumers will recognize such phrases as "the best" and "the world's best" as puffing in a given advertisement or commercial depends on how "the best" or "the world's best" is used and in what context, viewing the commercial as a whole. In other words, whether a claim is mere puffing is a question that can be determined only on the basis of what the commercial, as a whole, says.

308. In the Bayer commercials discussed in F. 305, *supra,* such phrases as "the best aspirin" or "the world's best aspirin" are more than puffing in the context of the commercials as a whole, for the commercials also did refer to the AMA and/or tests. Respondent's expert witness Dr. Haley agreed that "best" is not puffery when the claim is backed by scientific support (Haley, Tr. 10572). In fact, a large number of the viewers took the trouble to write in for the booklet mentioned in these commercials.

309. A good example of puffery is the tag line "Bayer works wonders" in a few of the pre-1970 Bayer advertisements in evidence. For example, CX 27 is a 1969 television commercial for Bayer (60 seconds) entitled "Ever Improved." The message of CX 27 is simply that no other OTC analgesic product is stronger or faster than "good old" Bayer Aspirin and that Bayer is good [**79**] for all kinds of aches and pains and fever—It works *wonders.* There is no suggestion in CX 27 that Bayer is superior, better or best for anything which might confuse or mislead consumers. It simply suggests that one cannot improve on good old Bayer Aspirin. When viewed as a whole, it is clear that "it works wonders" is a general praise and puffery not to be taken literally.

310. A dangling superlative is a claim that makes a comparison to another product without specifying the attribute being compared. The claim that "Bayer is the best aspirin" is a dangling superlative and thus invites the audience to supply the missing attribute. Dangling superlatives tend to confuse consumers by suggesting diverse inferences based on different plausible interpretations beyond the content of the incomplete statement (Miles, Tr. 9568–72, 9578–79, 9588–90).

311. In the case of a dangling superlative, what particular product attribute a viewer will supply in order to complete the incomplete comparison is often determined by the nature of the product involved. In the case of a dangling superlative in aspirin commercials, the

viewer will look for the unspecified attribute in terms of the primary function of the product involved.

312. Respondent's expert witness Dr. Russell Haley testified on direct examination as to how consumers would interpret the claim "best":

> What I was trying to say was the "best" is interpreted in the context of the category to which it applies. And so if you have a product which is supposed to do one specific thing, whatever that category is, and people are asked "What does it mean?" they will automatically respond with whatever the primary function of that product category is. So you can guess, if you know what the primary function of the category is, what the best thing is . . . In a therapeutic category it is curing whatever it is supposed to cure. (Haley, Tr. 10574)

313. The tag line used in a series of Bayer advertisements, "Aspirin is the best pain reliever and Bayer is the best aspirin" contains a dangling superlative "the best aspirin." However, the "best aspirin" claim follows the opening phrase "Aspirin is the best pain reliever." Thus the tag line as a whole clearly suggests that Bayer is the best pain reliever. *E.g.,* CX 48, 52, 157).

314. It is found that a substantial number of respondent's Bayer advertisements in evidence did not make the representation [80] alleged in Complaint Paragraph 10(A). They include, by way of examples, CX 73–78, 80–83, 105–108, 110–116, 162, 163.

315. For example, CX 78 is the storyboard of a 1973 television commercial (30 seconds) for Bayer Aspirin entitled "Woman's Place." The clear message of this commercial is that all aspirin is not alike and that Bayer's own test showed Bayer to be "the better quality aspirin." Throughout the commercial, every comparative (such as "better" or "superior") is qualified and clearly directed to "quality." There are no dangling superlatives or tag line closings which might confuse and mislead consumers to perceive this commercial as suggesting that Bayer is therapeutically superior to any other aspirin. It simply says Bayer is the "better quality aspirin" throughout the commercial. What it suggests is clearly that "you can count on Bayer," that Bayer will do what aspirin is supposed to do.

316. To cite another example, CX 75 (CX 75a) is a 1972 television commercial (30 seconds) for Bayer Aspirin entitled "Truisms." This was one of the two television commercials studied in the Zeisel Copy Tests (CX 520). The message is similar to that of CX 78 discussed above. Although the "quality" message is not as sharp as it is in CX 78, there is nothing in this commercial to suggest that it is talking about something other than Bayer's overall high "quality." It simply says "you can count on Bayer."

317. The Zeisel Copy Tests (CX 520) provides confirmatory evidence

with respect to CX 75 (CX 75a). Table 1 of the Zeisel study shows that about 4% of the respondents (subject to a sampling error of ±7%, assuming the sample were a probability sample which it was not) played back superior "effectiveness" message for Bayer in response to open-ended questions 2 and 3 (CX 520H, P, Z37).

318. CX 105 is the script of a 1972 radio commercial for Bayer Aspirin (30 seconds). The commercial tells the audience about a booklet that tells how Bayer "tested its aspirin for quality" against every leading brand and the tests showed "Bayer is better for quality." Another voice says Bayer is "a great product I can count on." The announcer tells the audience where to write for the booklet and says in closing "Find out why Bayer is the best quality aspirin." CX 105 is about "quality." The commercial expressly says Bayer is "a great product [one] can count on." Throughout the commercial, every comparative (such as "better" or "superior") is expressly qualified and directed to "quality." There are no dangling superlatives or unqualified comparatives that may confuse and mislead any listener to perceive this commercial as claiming superior therapeutic efficacy or safety for Bayer. There is nothing in this commercial to suggest anything other than product quality. [81]

319. CX 108 is the script of two 1972 radio commercials for Bayer Aspirin (30 seconds), recorded on the same day. Both versions (in identical language) talk about Bayer's better "quality" and state "I know I can count on [Bayer]." The announcer tells the audience where to write for the Bayer booklet and says in closing "Find out why Bayer is the best quality aspirin." Like CX 105, these commercials are about product quality and about Bayer being a product one can count on. Viewed as a whole, the advertisements do not suggest Bayer is "faster acting," "gentler," "more effective" or therapeutically superior in any other way to any other aspirin.

320. CX 162 is a 1973 print advertisement for Bayer Aspirin, Bayer-Timed Release Aspirin and Bayer Children's Aspirin. The message regarding Bayer Aspirin is that Bayer's own test showed for "quality" Bayer was superior and that "you can count on better quality Bayer." There is nothing in this advertisement to suggest anything other than "quality." The closing sentence expressly states "You can count on better quality Bayer."

321. It is found that an advertising claim that clearly and expressly says Bayer is the "better quality" aspirin or that Bayer can be counted on for "better quality" is a product quality claim and, as such, is distinguished from therapeutic superiority claims (such as "more effective," "faster acting" or "gentler" claim) discussed in F. 293–313, *supra.*

322. Product quality and high quality standards of manufacturers

are familiar concepts to consumers well-recognized in their daily experience, quite apart from the reason for being of the product category, which for aspirin is to relieve pain (Miles, Tr. 9328–29; John, Tr. 5586, 5592, 5594, 5596).

323. The underlying common sense reason for consumer recognition of the "product quality" concept is the consumer's natural desire that the product he or she purchases perform as expected and possess the attributes customarily associated with it—in other words that "it will do the job it is supposed to do" or "it can be counted on to perform as expected"; namely, "it will relieve pain and reduce fever." In fact, a number of Bayer product quality commercials discussed in this section expressly state that Bayer is "a great product you can count on" or "you can count on Bayer for better quality." In this sense, the concept of product quality with respect to aspirin is ultimately related to product performance, namely, the analgesic action. However, it is not reasonable to suppose that, therefore, a claim of superior product quality for aspirin will be understood by the consumer as meaning "superior therapeutic efficacy" in the same sense as a "stronger," "faster" or "gentler" claim for aspirin will be understood as meaning "superior therapeutic efficacy." The idea of quality has its own identity and content apart from the idea of efficacy, [82] although the two are ultimately related. In the former, product quality is a readily recognized, independent concept in the sense that it is universally thought to be a desirable attribute *for its own sake,* apart from the question of *more* or *less* pain relief (comparative efficacy). In the latter, "stronger" or "faster" has no meaning for aspirin users except in terms of "stronger pain relief" or "faster pain relief" (comparative efficacy). The idea of aspirin being "stronger" or "faster" can have no meaning other than "superior efficacy."

2. Complaint Paragraph 8(A)(1)

324. Sterling represented, directly or by implication, that it has been established that Bayer Aspirin is superior in terms of significant therapeutic effect to any other plain 5-grain aspirin. This representation was made in each of the advertisements listed in F. 136, *supra,* namely, CX 13, 15, 19, 37–39, 47, 48, 50–52, 54, 56–58, 60–67, 69, 70, 72, 74, 79, 99, 101–104, 109, 117, 122–129, 145–157, 150, 152, 155–158, 161.

325. The fact that the above representation was made is demonstrated by the advertisements themselves. The establishment representation in the challenged Bayer advertisements was made through a variety of methods and claims, including express statements, graphic support, and references to scientific studies or tests conveying the

impression that the underlying superiority claim for Bayer Aspirin was based upon strong medical or scientific fact (Ross, Tr. 5754–55).

326. Consumers tend to believe that when a claim of superior efficacy is made for a drug product, there exists a strong basis in medical-scientific fact for such claims. Scientific fact means that the fact or proposition has been accepted by the scientific community as a fact. When analgesic advertisements make claims of superior efficacy to other aspirin, they also represent, by implication, that the fact of superior efficacy has been established (Ross, Tr. 5756–57).

3. Complaint Paragraph 20

327. Sterling represented, directly or by implication, that Bayer Aspirin has been tested against 220 other brands of aspirin for quality, purity, freshness, stability and speed of disintegration and that the the results of the tests demonstrated that Bayer Aspirin is qualitatively superior to all other brands tested in all tested respects and therapeutically superior to all other brands tested. This representation was made in the following advertisements: CX 48, 50, 52, 54, 56, 58, 60–63, 67, 72, 74, 79, 102, 104, 155–158.

328. The fact that the advertisements listed in the preceding Finding made the claim alleged in Complaint Paragraph 20 is evidenced by the advertisements themselves. [83]

329. They not only claim, directly or by implication, that Bayer is therapeutically superior to other aspirins (for the reasons discussed hereinabove in connection with Complaint Paragraph 10(A)), but also refer to the so-called "223 test" and mention such factors as quality, purity, freshness, stability, and speed of disintegration, in varying combinations. A narrow interpretation of these advertisements is that the results of the 223 test showed that Bayer was qualitatively superior with respect to each of the attributes being expressly named in a particular advertisement.

330. However, it is also reasonable to interpret these same advertisements to mean that the results of the "223 test" showed that Bayer was superior overall for the tested attribute, including the factors not being expressly named. CX 155 (a print advertisement) is a good example. CX 155 says 221 brands were tested in 30 different ways and Bayer "was superior . . . showing greater stability, purity and freshness," and "no other aspirin tested met the overall high standards set by" Bayer.

4. Complaint Paragraph 15(A)

331. Sterling has represented in a very small number of advertisements that Bayer Aspirin relieves nervous tension, anxiety and irritability and improves the user's mood. This representation was made in

three television commercials (CX's 29, 30 and 33) and two print advertisements (CX 141 and CX 151).

332. CX 30 (CX 30a) is a 1969 television commercial (60 seconds) for Bayer entitled "Summer." This is a good example of how a television commercial, while the announcer speaks of headache pain relief, can also imply a distinct message of tension relief to the audience through a depiction of situational tension by the use of audiovisual technique that is uniquely television's.

333. CX 30 (30a) begins by depicting, through pictorial images and sound, a tense situation where a mother is supervising a noisy and crowded swimming pool party on a hot summer day, drying children, serving snacks. The picture shows an obviously harrowed, tense mother. What follows is the announcer's voice, against appropriate pictorial backgrounds, narrating what Bayer Aspirin can do for you when you have a "hot weather headache" and accompanying "tension" and "irritation." While the voice gives the direction, the mother reaches for Bayer, takes two tablets with a glass of water, lies down on a chaise, and returns to the party to cook hot dogs, relaxed and refreshed. Although the spoken message is innocuous, a viewer of this television commercial will come away with a distinct "tension relief" message apart from pain relief because of the very strong and effective audiovisual suggestion of a situational tension throughout the commercial. [84]

334. Confirmatory evidence of consumer understanding of CX 30 is found in the consumer responses to "A Qualitative Assessment of Recent Bayer Aspirin Commercials," by Dancer-Fitzgerald-Sample, one of Sterling's advertising agencies at the time. The moderator of a focus group viewing CX 30 found that "something about the situation portrayed seemed to emphasize tension at the expense of headache." Quotes from participants describing their recall of CX 30 include:

there was a real nervous feeling;

she built up tension with all the shouting and running around;

to me, it was much more of a nervous strain than a headache;

and her problem is nervous tension which is something all women have. (Miles, Tr. 9642–44).

335. CX 29 (29a) (a 60-second television commercial), CX 138 (a 30-second radio commercial) and CX 150 (a print advertisement) depict Bayer Aspirin as relieving sleeplessness due to small pains by relieving pain. The spoken message in CX 138 and the printed message in CX 150 are straightforward. There is no suggestion that Bayer

will make you sleep or relieve your tension in either CX 138 or CX 150. Taking each advertisement as a whole, a listener or reader is not likely to come away with a perception that these advertisements are claiming that Bayer is a sedative or tension relieving product. Although one cannot exclude the possibility that mere mention of the word "sleep" or "sleepless" in an advertisement may evoke a perception of sedation or tension relief, that possibility is remote with respect to CX 138 and CX 150, which clearly and repeatedly state that Bayer helps by relieving little aches and pains.

336. CX 29, however, is a television commercial and begins with magnified and persistent sound of a dripping faucet against pictorial images of a late night bedroom-bathroom scene, which depict a couple trying to sleep and obviously disturbed by the dripping faucet. This audiovisual sequence effectively establishes a situational tension before little aches and pains are mentioned. The message that Bayer is good when you are having trouble sleeping because of minor discomforts and little aches comes through clearly. At the same time, because of the opening audiovisual sequence which effectively evokes a lingering image of situational tension, viewers may reasonably perceive this television commercial as also claiming tension relieving action for Bayer. [85]

337. CX 141 is a Bayer print advertisement. Its main message is that Bayer is good for hot weather headaches. However, the printed words carry a distinct undertone of mood alteration apart from headache relief. They claim in explicit terms that when you are "in no mood to enjoy life or the company of others because you "feel so headachy and edgy that the simplest chore, the smallest disturbance becomes an irritation" you can "turn that mood around" by taking two Bayer Aspirin, sitting down and relaxing for a few minutes. A reader may reasonably perceive this print advertisement as also saying that Bayer can turn around one's mood apart from headache relief.

338. CX 151 is a Bayer print advertisement. It has two main messages: (1) that Bayer is good for "tension-caused headaches and general achiness," and (2) that Bayer is a high quality aspirin. The express claim that Bayer will relieve "tension-caused headaches" is confusing and strongly suggestive of "tension relief." It is reasonable to conclude that very few, if any, consumers will understand "tension-caused headache" as meaning "muscle-tension headache" and that most consumers will reasonably perceive a "tension relief" claim apart from headache relief in this advertisement.

C. Specific Allegations Related to Bayer Children's Aspirin Advertising

1. Complaint. Paragraph 10(B)

339. Sterling has represented that Bayer Children's Aspirin ("BCA") is superior in terms of significant therapeutic effect to any other children's aspirin. This representation was made in CX 167–170, 175–185, 188, 194–198, 201–203, 205, 209.

340. A number of BCA advertisements make a therapeutic superiority claim by representing, expressly or by implication, that BCA is faster-acting and/or gentler than other children's aspirin. Such advertisements include CX 182–184, 209.

341. For example, CX 182 (182a) is a 1972 television commercial for BCA entitled "Behind You" (30 seconds). Although the main theme of the commercial is BCA, made by the maker of Bayer Aspirin, is a high quality children's aspirin. However, by expressly claiming that the blending of two kinds of aspirin crystals instead of one results in a smooth and gentle disintegration, the advertisement strongly suggests that, therefore, BCA is faster-acting and more gentle than other children's aspirins, which use only one shape of aspirin crystals.

342. In CX 184 (184a), a 1972 television commercial for BCA entitled "Slide" (30 seconds), the therapeutic superiority claim is made in a way similar to CX 182. CX 184 also suggests that the blending of two shapes of aspirin crystals instead of one [86] makes BCA go to work quickly and gently. Many consumers will reasonably perceive this commercial as claiming that BCA is a faster-acting and more gentle aspirin than others, which use only one shape of aspirin crystal. CX 209, a 1973 print advertisement for BCA, is similar to CX 183 and 184 in that it also refers to the blending of two shapes of aspirin crystals instead of one and suggests BCA is a faster-acting and gentler aspirin than others.

343. A small number of BCA advertisements expressly claim that BCA is made differently or uses a unique (or special) manufacturing process and thereby imply that BCA is therefore therapeutically superior to other aspirins. Such advertisements include CX 167, 175, 181, 183, 188, 195, 197, 203, 205.

344. A claim that BCA is "made differently" or that "no one makes aspirin like Bayer" or that BCA uses a "unique (or special) manufacturing process" is ostensibly directed to manufacturing process and thus related to product quality. However, such claims go beyond saying "BCA is a high quality product you can count on" or "BCA will do what you expect of children's aspirin to do" and further suggest a comparison in terms of therapeutic performance. Many consumers will reasonably perceive such claims as saying that because Bayer

uses a "special" or "unique" process no one else has, Bayer (BCA) is therapeutically superior to others.

345. A substantial number of BCA advertisements tie the best care parents wish to give to a sick child with an express claim that BCA is the best children's aspirin. They include CX 167–170, 175–181, 185, 194–198, 201–203, 209.

346. For example, CX 176 (176a), a 1968 television commercial for BCA entitled "Mother Knows" (60 seconds) begins:

> Sneezes, runny noses, temperature—a hundred and one. The doctor says its a cold . . . and a mother knows what to do. She keeps the patient quiet . . . and she gives her children aspirin . . . to reduce the fever and relieve the aches.

CX 176 then continues:

> She chooses Orange Flavored Bayer Aspirin for Children—because she knows Bayer makes the best children's aspirin . . .

Such "best" claims represent to consumers that the product is therapeutically superior to the other pain relievers it is being compared to, in this case, all other children's aspirin in the same manner discussed earlier in connection with Bayer Aspirin advertisements making "the best" claim (F. 305, *supra*). [87]

347. It is found that a number of BCA advertisements in evidence did not make a therapeutic superiority claim, although they contain a claim of superior product quality for BCA. Such advertisements include, for example, CX 162, 163, and 187. These advertisements contain claims regarding quality control ("made with extra care," "200 tests," "highest standards"), which are directed to "product quality." "Product quality" and "quality control" are concepts familiar to and readily recognized by purchasers of analgesic products and are distinguished from such therapeutic superiority claims as "stronger," "faster-acting" and "gentler." (*See* F. 314–323, *supra*).

2. Complaint Paragraph 8(A)(2)

348. Sterling has represented that it has been established that BCA is superior to any other children's aspirin in terms of significant therapeutic effect (Complaint Paragraph (8)(A)(2); CX 167–170, 175–185, 188, 194–198, 201–203, 205, 209).

349. The representation that the therapeutic superiority of BCA has been established is explicitly contained in the BCA advertisements which assert specifically that the crystalline composition of the aspirin in BCA is different from that in any other children's aspirin, and that this difference results in improved therapeutic performance. For example, in CX 184, actress Jane Wyatt states:

I know what it's like being a mother. Only the best is good enough. So when you child gets a cold or flu, you should know that every children's aspirin tablet is made up of tiny crystals. But instead of using just one shape of crystal, Bayer Children's Aspirin blends two shapes . . . to help it go to work quickly and gently. I'm Jane Wyatt and I know that if Andy (holds baby) were my child I'd give him children's Bayer.

This advertisement clearly conveys the impression of a type of superiority grounded in accepted scientific fact. Similar representations are made in CX 182, 183, 209.

350. The references to and depictions of the unique manner in which a product is manufactured conveys to consumers the impression that the superiority of that product has been established (Ross, Tr. 5757). Such establishment representations by references to the unique or special manner in which BCA is made are found in CX 167, 175, 182–185, 188, 195–197, 203, 205, 209.

351. In addition, each of the BCA advertisements listed in F. 348, *supra* as making a claim of therapeutic superiority for [88] BCA also represented, by implication, that such therapeutic superiority has been established, for the reasons discussed earlier in connection with Bayer Aspirin advertisements claiming therapeutic superiority for Bayer Aspirin (F. 326, *supra*).

D. *Specific Allegations Relating To Vanquish Advertising*

1. Complaint Paragraph 12(B)(1)

352. Sterling represented that a recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin. This representation was made in CX 224, 226, 235–236, 241–247, 250–256, 258–264.

353. Vanquish has been portrayed as more effective than the leading "extra strength" tablet because Vanquish contains other extra ingredients (CX 252–253, 256, 258, 264). In other instances, Vanquish is depicted as a special "extra strength" product (CX 245–247, 250–252). The clear implication of such claims is that, because of Vanquish's "extra strength," it is more effective than other analgesics. Sterling's witness Dr. Miles agreed that such "extra strength" claims represented to consumers that the product is superior in terms of efficacy (Miles, Tr. 9495–97). Similar "extra strength" or "extra ingredients" claims are also made in CX 224, 226, 236, 241–244, 259–263.

354. A number of Vanquish advertisements depict the product as being so special or effective that, in contrast to other pain relievers, one's headache should not come back after taking Vanquish (CX 224, 226, 235, 241–243). The clear impression of such advertisements is that Vanquish is more effective than other analgesics.

355. Vanquish has also been depicted as having a unique, different, or special formula (CX 224, 226, 235, 236, 241–247, 250–251). Such claims of uniqueness may reasonably be interpreted by consumers as meaning that Vanquish is more effective than the recommended doses of other aspirins.

2. Complaint Paragraph 8(B)(2)

356. Sterling has represented that it has been established that a recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin. This representation was made in CX 224, 226, 235, 236, 241–247, 250–256, 258–264. All such advertisements make the core representation that Vanquish is more effective than aspirin. [89]

357. The Vanquish advertisements depict the superiority of Vanquish in conjunction with various indicia of scientific establishment. For instance, various advertisements depict the formulation of Vanquish with chemist's instruments (CX 224, 226, 241–244). Vanquish has been characterized as containing "two *medically-proven* ingredients" (CX 254), or as combining the "*proven* effectiveness of aspirin with other *powerful* ingredients" (CX 224). Such advertisements convey the impression that Vanquish's superiority has been predicated upon scientific or medical fact.

358. Because the advertising claim alleged in Complaint Paragraph 8(B)(1) has not been scientifically established in accordance with the standards established and adhered to by qualified experts in the scientific community, the claim was made in the face of substantial question as alleged in Complaint Paragraph 13.

3. Complaint Paragraph 12(C)

359. Sterling has represented that a recommended dose of Vanquish is more effective for the relief of pain than the largest selling "extra strength" tablet. This representation was made in CX 252–253, 255–256, 258–264.

360. CX 252–253, 255–256, 258–264 all explicitly compare the effectiveness of, or ingredients in, Vanquish to the leading or largest selling "extra strength tablet." Such advertisements claim that Vanquish has "more pain relievers" than the largest selling tablet. A clear implication of such claims is that Vanquish, because it contains "more pain relievers," is more effective than the extra strength tablet. Dr. Miles, Sterling's witness, agreed that consumers perceive the claim that a product "has more pain-relieving ingredients" to mean that the product is more effective (Miles, Tr. 9495–96).

4. Complaint Paragraph 8(C)

361. Sterling has represented that it has been established that a recommended dose of Vanquish is more effective for the relief of pain than the largest selling "extra strength" tablet in CX 252–253, 256, 258–264.

362. CX 252–253, 255–256, 258–264 represent that Vanquish is more effective than the largest selling extra strength tablet. All such advertisements explicitly compare Vanquish's superiority to another drug. Since each of these Vanquish advertisements makes a claim of comparative efficacy over another drug, such Vanquish advertisements represent to consumers that such superior efficacy has been established for the same reasons discussed earlier in connection with certain Bayer Aspirin advertisements containing a superior efficacy claim (F. 326, *supra*). **[90]**

5. Complaint Paragraph 12(B)(2)

363. Sterling has represented that because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any nonprescription internal analgesic not containing buffers in CX 224, 226, 235–236, 241–247, 250–256, 258–264.

364. For example, in CX 245 (245a), a television commercial for Vanquish entitled "Tuesdee Testa" (60 seconds), a female jockey is depicted as looking for a strong analgesic with "gentle action." CX 245 states that "Vanquish is different from the others." Vanquish is then compared to the "leading extra strength pain reliever" which has no buffers. The advertisement then concludes that Vanquish "gives you extra strength and gentle buffers" and that it is "gentle enough to your system." The clear implication of such claims is that Vanquish is more gentle on the stomach because it contains "gentle buffers."

365. CX 247 (247a) is a television commercial for Vanquish entitled "Round Ones" (60 seconds). It compares three leading pain relievers, including the extra strength product without buffers, with Vanquish and states that "Vanquish gives you extra strength and gentle buffers. It's the only leading pain reliever you can buy that does." The advertisement then concludes with the claim that Vanquish gives you extra strength "yet is gentle enough for your system." Similar claims are found in slightly varied form in CX 246, 250 and 251).

366. A number of Vanquish advertisements claim that Vanquish has "two buffers" (CX 224, 226, 252, 253, 255, 256, 258–260), "gentle buffers" (CX 236, 241, 242, 244–247, 250, 251, 261–264), or "buffers" (CX 235, 243). References to Vanquish containing "gentle buffers" are also made on the Vanquish package which is conspicuously displayed in many of the Vanquish advertisements (*e.g.*, CX 254, 255, 258–264).

Consumers would understand such references to the presence of "buffers" in Vanquish to mean that buffers are put in Vanquish to reduce the incidence of gastric discomfort (Ross, Tr. 5792, 5800–01). Thus, the advertisements set forth in F. 363, *supra,* represented that because Vanquish contains gentle buffers, it will cause less gastric discomfort than any other nonprescription internal analgesic not containing buffers.

6. Complaint Paragraph 8(B)(2)

367. Sterling has represented that it has been established that because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any nonprescription internal analgesic not containing buffers. This representation was made in CX 224, 226, 235, 236, 241–247, 250–256, 258–264. [91]

368. The advertisements set forth in the preceding Finding make the core representation that because Vanquish contains buffers it will cause less gastric discomfort than any other internal analgesic not containing buffers. In addition, various such advertisements contain references to science, and language which communicates the impression that the claims have been established as scientific or medical fact. For instance, while the language of various advertisements represents Vanquish as giving the "proven effectiveness of aspirin" with "buffers," the video portion of these ads depicts the formulation of Vanquish with chemist's instruments, such as the mortar and pestle (CX 224, 226, 241–244). Vanquish is also explicitly represented as a "more complete formula, designed for more complete relief." (CX 235, 236, 243, 244). Reference to a unique or special formula specifically designed for greater relief implies that the composition of Vanquish is the end product of a scientific or medical inquiry which developed a formulation superior in terms of efficacy and freedom from side effects.

369. Since each of the Vanquish advertisements set forth in F. 363, *supra,* makes a comparative superiority claim over another drug, they also represented to consumers that such superiority has been established for the same reasons discussed in connection with comparative efficacy claims made for Bayer Aspirin (F. 326, *supra*).

7. Complaint Paragraph 23

370. Upon a review of the Vanquish advertisements in evidence, Sterling (except in CX 224) did not mention that Vanquish contains aspirin. Therefore, Sterling failed to disclose that Vanquish contains aspirin (Non-Contested Issue 18; CX 226, 235, 236, 241–247, 250–256, 258–264).

371. Sterling believed that disclosing in advertising the aspirin

content of Vanquish would remove a "valuable mystique" of that product (CX 485).

E. *Specific Allegations Related To Cope Advertising*

1. Complaint Paragraph 12(A)

372. Sterling represented that Cope was more effective for relief of "nervous tension headache" pain than a recommended dose of all other nonprescription internal analgesics. This representation was made in CX 272–276, 283, 287, 293–294.

373. For example, CX 272, a 1970 television commercial for Cope entitled "Important" (30 seconds), states that for the relief of "nervous tension headaches . . . a combination of **[92]** pain reliever and a sedative provides *greater relief* than either medication alone." (emphasis added). Sterling witness Dr. Miles agreed that promises in analgesic advertisements of greater or more complete relief were perceived by consumers as promises of superior effectiveness (Miles, Tr. 9494–97). CX 272 next states that *only* Cope contains this combination of ingredients. Thus, because the advertisement claims that Cope, and only Cope, contains this special combination, a reasonable interpretation is that Cope is more effective for the relief of "nervous tension headaches" than a recommended dose of any other nonprescription internal analgesic. This representation is also made in a similar manner in CX 273–275, 283, 287, 292–294.

374. Similar superiority claims have been made in other Cope advertisements characterizing Cope's formulation for the relief of the nervous tension headache as "unique," or "uncommon" (CX 273–275, 292–294). These claims of uniqueness imply that Cope's special formulation provides superior nervous tension headache relief to any other analgesic.

2. Complaint Paragraph 8(A)(3)

375. Sterling has represented that it has been established that a recommended dose of Cope is more effective for the relief of "nervous tension headache" pain than other nonprescription internal analgesics. This representation was made in CX 272–276, 283, 287, 292–294).

376. The Cope advertisements listed above include explicit references to scientific findings, as well as language representing that the efficacy claim is based upon scientific or medical fact. For example, CX 272, 283, and 287 portray the efficacy claims for Cope as having been proved by "important studies made at the world's leading headache clinic" which "show" that Cope's formulation provides superior efficacy. This message clearly represents that the superiority claim has been proved or established by appropriate scientific testing.

377. Cope also has been portrayed as containing a unique formula, specifically developed for the relief of a special type of pain—the nervous tension headache. Some Cope advertisements have claimed that the Cope formula is "unique" (CX 274, 275, 292–294). These claims clearly imply that Cope is the end product of scientific evaluation proving that the "unique" ingredients in Cope provide superior relief for "nervous tension headache."

378. Each of the Cope advertisements set forth in F. 375, *supra,* contains an implied claim of comparative efficacy for the same reasons discussed in connection with Bayer Aspirin advertisements (F. 326, *supra*). **[93]**

3. Complaint Paragraph 18

379. Sterling has represented that, by referring to the results of tests or studies in Cope advertisements, such tests or studies prove the claim that a recommended dose of Cope is more effective for the relief of "nervous tension headaches" than recommended doses of all other nonprescription internal analgesics. This representation was made in CX 272, 283, and 287.

380. CX 272, 283, and 287 state explicitly that "important studies made at the world's leading headache clinic show that for the relief of severe nervous tension headaches," the formulation in Cope provides the greatest amount of relief. These three advertisements thus represented that tests or studies prove Cope's superiority for the relief of the nervous tension headache.

4. Complaint Paragraph 22

381. Sterling has represented that Cope contains a unique formula in that it alone among nonprescription headache remedies contains both a pain reliever and an ingredient with sedative properties. This representation was made in CX 272–276, 283, 287, 292–294).

382. For example, CX 272 represents that Cope contains a unique formula: "Of all leading remedies you can buy, only Cope combines a gentle relaxer with a powerful pain reliever." Other Cope advertisements expressly represented that Cope contains a "unique" (CX 274, 275, 292–294) or "unduplicated" (CX 273) formula because it alone combines a pain reliever with a sedative ingredient. Thus, Sterling has represented in such advertisements that Cope's formula is unique in that Cope alone contains both a pain reliever and a sedative.

383. The Cope advertisements making the representation alleged in Complaint Paragraph 22 were disseminated to the public between January 1969 and June 1971 (CX 633). Excedrin PM was introduced into two test markets in February 1969 and was then marketed nationally beginning in August 1969 (CX 638, admission 1069).

5. Complaint Paragraph 15(B)

384. Sterling has represented that Cope relieves nervous tension, anxiety and irritability and will enable persons to cope with the ordinary stresses of everyday life. This representation was made in CX 272–276, 283, 287, 292–295.

385. Cope has been portrayed in CX 272–276, 283, 287, 292–294 as specially formulated for relief of the "nervous tension headache." A reasonable implication of this claim is that Cope will help relieve not only the pain associated with nervous [94] tension but also other symptoms associated with stress, such as anxiety and irritability.

386. For example, in CX 276 (276a), a 1970 television commercial for Cope entitled "Headache Three" (30 seconds), three persons at work are portrayed, through the use of audiovisual technique, as being in a stressful situation. A grimacing mother, with one hand stroking her forehead, says, "I get it on rainy days." A traffic policeman, with a similar gesture, says, "I get it during rush hour." A secretary, after showing a man looking over her shoulder, says with an harrassed look, "I get it when the boss looks over my shoulder." Then the announcer, against a blow-up of Cope tablets and package, says:

> When the name of the pain is nervous tension the name of the remedy is Cope, because Cope gives you a powerful pain reliever plus a gentle relaxer. Yes, when the name of the game is nervous tension headache the name of the remedy is Cope.

Most viewers of CX 276 will come away with an implied but unmistakable claim that Cope is the right remedy not only for tension-headache pain but also for nervous tension and anxiety apart from headache.

387. In CX 292, 293 and 294 it is expressly stated:

> a proven relaxer with the pain reliever doctors recommend, so two tablets work on both parts of your tension headache: the tension *and* the pain. In fact, Cope helps ease tension throughout your body, so you can relax and feel like yourself again [emphasis in original].

The clear implication of such representations is that Cope will relieve nervous tension and allow the user to better cope with stress. Such representations would be understood by consumers to mean that Cope relieves tension and related stress and anxiety wholly apart from any ability to relieve headache pain.

6. Complaint Paragraph 24

388. A review of the Cope advertisements in evidence shows that Sterling did not mention the fact that Cope contains aspirin in any

of the advertisements. Thus Sterling failed to disclose that Cope contains aspirin (Non-Contested Issue No. 18; CX 272–276, 283, 287, 292–294). [95]

F. *Specific Allegations Relating To Midol Advertising*

1. Complaint Paragraph 15(C)

389. In the advertisements for Midol in evidence, Midol has been expressly and consistently represented as a product developed especially for women's periodic pain and menstrual discomfort. None of the Midol advertisements claim, directly or by implication, that Midol will relieve any condition for anyone other than menstruating women. *See* CX 296A, 297–306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053.

390. In many of the Midol advertisements, it was represented that Midol will relieve nervous tension, stress, fatigue and depression related to menstruation and improve the mood of menstrual women (CX 296A, 297–300, 303, 306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053).

391. In CX 296A, a 1969 television commercial for Midol entitled "Wood & Stream" (30 seconds), Midol is represented as a product that "calms jumpy nerves" and is effective in fighting depression because "the overall action of Midol chases the blues away." Midol is further positioned as fighting the fatigue associated with menstruation because it allows the user during the period to "be an active girl, nonstop. No slow down." Thus, the advertisement clearly conveys the suggestion that use of Midol will improve menstrual women's mood. Similar claims, including virtually identical language, are found in CX 297–300, 303.

392. A review of the verbatim responses to CX 441, a Burke copy test of CX 296A, confirms that some female viewers perceived the claims in CX 296A as promising that Midol will relieve nervous tension, stress, fatigue, depression accompanying menstruation and improve women's mood during menstruation. In CX 441, responses included playbacks of themes relating to Midol's ability to relieve tension and depression. Such playbacks included: "it helps the headache and blues," "you don't feel blue" (CX 441F), "being for pain and to relieve tension and the blues" (CX 441G), "you don't feel under tension and makes you less nervous," "it relieves tension," "help ease and relax you," "you won't be nervous or depressed if you use Midol" (CX 441H), "it helps you get over the blues . . . . keeps you from being down in the dumps," "use it for depression and minor things like that" (CX 441I), "it relieves pain and tension," and "for cramps and tension" (CX 441J).

393. Similar tension and mood altering representations are found in the Midol print advertisements in evidence (CX 306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053). In CX 306E, for example, Midol is portrayed **[96]** explicitly as containing "a mood brightener" which gives you a real lift . . . helps you go through the day cheerfully, alert."

394. Similar "mood brightener" language is found in all the Midol print ad in evidence. This impression is reinforced by the "before and after" pictorial representation in such advertisements as CX 306, 306A, B and C where Midol users are portrayed as "dismal," "sunk," "tense," or "blue" before taking Midol, but "bright," "saved," "happy," or "gay" after taking Midol.

2. Complaint Paragraph 26

395. Sterling has represented that the analgesic ingredients in Midol are other than ordinary aspirin and the stimulation in Midol is other than caffeine (CX 296A, 297–300, 303, 306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053).

396. Sterling has explicitly claimed that Midol's formula is unique or exclusive. For example, in CX 296B Midol is portrayed as having "an exclusive formula with medication ordinary pain relievers don't give you." This language clearly suggests that Midol's active ingredients are something other than aspirin (which is the active ingredient in the "ordinary pain relievers" with which Midol is being contrasted) and caffeine. Similar representations of uniqueness of formulation are made in CX 297, 300–302, 304, 306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053.

3. Complaint Paragraph 25

397. A review of the Midol advertisements in evidence shows that they did not mention that Midol contains aspirin. Therefore, Sterling failed to disclose that Midol contains aspirin (Non-Contested Issue of Fact No. 18; CX 296A–B, 297–300, 303, 306, 306A–C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053).

G. *Allegations Regarding Inconsistent Claims (Complaint Paragraph 17)*

398. Sterling has represented that Bayer Aspirin is as effective for the relief of headache pain (including "nervous tension headache" pain) as, and will cause gastric discomfort no more frequently than, any other nonprescription internal analgesic, including Cope and Vanquish (Complaint Paragraph 17(A); CX 3, 11, 14, 15, 17–21, 25, 31, 34, 35, 44, 45, 47, 48, 50, 52–64, 70, 88–91, 94, 97, 100–104, 118–123, 131, 140, 142–144, 153–156).

399. Sterling has represented that Cope is more effective for the relief of the "nervous tension headache" pain than any other nonprescription internal analgesic, including Bayer [97] Aspirin and Vanquish (Complaint Paragraph 17(B); CX 272–276, 283, 287, 293–294). *See* F. 372–374, *supra.*

400. Sterling has represented that Vanquish is more effective for the relief of headache pain than aspirin, including Bayer Aspirin, and will cause less gastric discomfort than any nonbuffered internal analgesic, including Bayer Aspirin (Complaint Paragraph 17(C); CX 224, 226, 235, 236, 241–247, 250, 255, 256, 258–264). *See* F. 352–369, *supra.*

401. The Bayer advertisements set forth in F. 398 were disseminated through national media from April 1969 through September 1972 (CX 630). The Cope advertisements set forth in F. 399 were disseminated through national media from January 1969 through June 1971 (CX 633). The Vanquish advertisements set forth in F. 400 were disseminated through national media from April 1969 through December 1974 (CX 632).

402. The representations made as alleged in Complaint Paragraphs 17(A), (B), and (C) are mutually inconsistent.

403. From April 1, 1969 through June 1971, Sterling disseminated through national media contemporaneous and inconsistent claims regarding Bayer, Cope, and Vanquish. Contemporaneous and inconsistent claims regarding Bayer Aspirin and Vanquish continued until September 1972.

404. Advertising proposals for products manufactured by Sterling are developed by advertising agencies which present proposed advertisements to the company for approval. Such approval must be obtained prior to any dissemination of the advertising (Alberts, Tr. 8998–99). Sterling maintains an established advertising approval procedure in which each prospective advertisement is reviewed by various company officials. The purpose of this advertising review procedure is to ensure that all advertising claims are accurate and that medical and scientific substantiation is adequate (John, Tr. 5576–79; Alberts, 8998–9000).

405. Sterling's process for reviewing analgesic advertising claims is as follows: The product manager for the particular product and the advertising agency for the product will design a proposed advertisement, portions of which are submitted to appropriate personnel for verification even prior to the formal approval procedure. That proposed advertisement will be put in the form of either a transcript or a storyboard or both and circulated in succession among specified people at Sterling for approval. Persons who must approve the proposed advertisement by placing their initials on a written form

include the Product Manager, the Group Product Manager, the Medical Director of Glenbrook Laboratories, the legal department, the President of Glenbrook Laboratories, and the Vice President for Sales or Marketing (John, Tr. 5576–79; Alberts, Tr. 8998–9000; G. Goldstein, Tr. 14784–85; Mattimore, Tr. 15359–60; CX 536). [98]

406. At each stage of the advertising review process, Sterling had professionals with expertise in their various fields exercising their best judgment as to whether claims in the advertising were supportable from a medical, advertising/marketing, or legal standpoint (John, Tr. 5577–81; Alberts, Tr. 8998–9000; Mattimore, Tr. 15359–60). For example, to determine the correctness of, and substantiation for, any scientific claim, whether pharmaceutical or medical, those responsible for reviewing and advertisements had access to inhouse Sterling experts, including pharmaceutical experts at the Bayer plant and scientists at the Sterling-Winthrop Research Institute, as well as access to outside experts. With respect to substantiation of medical or therapeutic claims, the Medical Director of Glenbrook Laboratories was the principal official directly responsible for the matter (Alberts, Tr. 8998–9000; G. Goldstein, Tr. 14785–90; Mattimore, Tr. 15361; Trout, Tr. 16089–90).

407. It was standard procedure for marketing personnel involved in the advertising review process to refer, for accuracy and substantiation, all proposed claims and statements relating to Bayer's pharmaceutical quality, pharmaceutical standards and manufacturing standards to Sterling's experts at its Trenton plant: Mr. Winig, head of the Trenton plant during the period involved in this case, or Mr. Mannix, then Director of Quality Control, or other knowledgeable persons (Alberts, Tr. 8998–9000 Mannix, Tr. 14634; Winig, Tr. 14759–61 Mattimore, Tr. 15359, 15361; Trout, Tr. 16089–90). Mr. Winig also was a member of the executive committee that approved all advertising (Winig, Tr. 14759).

408. In addition to access to scientific experts, all Sterling personnel responsible for advertising substantiation have access to Sterling's library resources (G. Goldstein, Tr. 14786–90; Mattimore, Tr. 15361; Trout, Tr. 16090–92). Among Sterling's libraries are those located at corporate headquarters in New York City and at the Sterling-Winthrop Research Institute in Rensselaer, New York. The Sterling-Winthrop Research Institute library is a resource for the approximately 700 scientists employed at the Institute (G. Goldstein, Tr. 14729, 14736–37). The library staff researches any subject requested by Sterling personnel by reviewing treatises, texts and published literature (G. Goldstein, Tr. 14730).

409. According to Sterling's officials, the Sterling librarians keep abreast of medical and scientific journals and are linked by computer

to the National Library of Medicine. A service of the American College of Physicians reviews literature on various products for the Sterling libraries. The Sterling [99] library in England reviews all European literature and translates important articles for transmission to the United States. The Sterling library itself generates a monthly abstract of important literature, including summaries of articles relating to analgesic products and ingredients, which is sent to top management, medical personnel, and appropriate marketing personnel. The full text of the summarized article is supplied to Sterling personnel upon request (G. Goldstein, Tr. 14730–37; Trout, Tr. 16090–92).

410. Sterling's medical and pharmaceutical personnel involved in the advertising review process often attend conferences, seminars and professional meetings. At such activities, papers are presented, including materials or studies either not yet published or that may never be published (G. Goldstein, Tr. 14801–02, 14844–45, 14849, 15058–59, 15061–64; RX 148).

411. It is fair to conclude that respondent, through its own resources or through arrangements with other institutions, has access to a large body of published literature, including books and treatises, that exist in the field of mild analgesics. It is Sterling's position that, through efforts by Sterling library personnel and otherwise, Sterling personnel directly involved in or consulted about substantiation keep abreast of current developments relating to mild analgesics (John, Tr. 5706–07, 5576–77; G. Goldstein, Tr. 14734–36, 14785–90).

412. In 1973 the FTC served a subpoena upon respondent requesting substantiation materials for the challenged advertising claims. In response to this subpoena, some documents were produced, dated through December 31, 1973. As part of this 1973 subpoena response, incorporated by reference, were substantiation documents produced to the Federal Trade Commission by respondent in response to prior subpoenas in 1966 and 1971 (G. Goldstein, Tr. 14834–38).

413. As part of such substantiation materials, a large number of documents were produced which included many published articles in the scientific literature and summaries and excerpts of such literature (*e.g.*, RX 185; G. Goldstein, Tr. 14814–15). It is Sterling's position, taken at trial, that not all of the substantiating literature that Sterling had knowledge of and relied upon was produced at that time, as this would have been physically impossible and that only representative materials were produced (G. Goldstein, Tr. 14840). [100]

IV. THE SCIENTIFIC EVIDENCE SUPPORTS THE ALLEGATIONS OF THE COMPLAINT

A. *Sterling Did Not Have A Reasonable Basis For Its Claim That Bayer Aspirin Is Qualitatively Or Theraputically Superior Or That Such Claims Have Been Scientifically Established*

1. Well-Controlled Clinical Studies Are Necessary to Establish the Comparative Efficacy or Safety of Analgesic Drugs

414. In order to consider any scientific or medical proposition as established, experts in the pertinent field must be convinced that the proposition is proven or sufficiently supported by a type and quality of evidence that reduces the chance for error to an acceptable minimum and is unlikely to be due to chance (Moertel, Tr. 6309). In this connection, experts apply a set of well-controlled methodological and analytical criteria in order to determine whether a given body of evidence is sufficient to establish a proposition (Moertel, Tr. 6255; Grossman, Tr. 7767–69).

415. The record shows that Sterling also understood and used the term "established" in the same sense in documents dated January 7, 1957 and filed with the Federal Trade Commission protesting the adequacy of scientific substantiation for certain of its competitor's advertising claims for OTC analgesic products. In discussing the results of a clinical test comparing Bufferin and Bayer Aspirin and conducted by a well-known investigator, Sterling maintained that, "he [the investigator] recognizes the 'possibility' that Bufferin might be a little more irritating than Bayer aspirin but the figures were not sufficiently significant to establish this" (CX 371Z002).

416. The only type of evidence sufficient to establish the comparative efficacy of drugs is developed through well-controlled clinical tests using real patients with real symptoms (Moertel, Tr. 6255; Grossman, Tr. 7459, 7482; DeKornfeld, Tr. 8388–89; Feinstein, Tr. 16413, 16441–44; CX 466, p. 35371, 35444).

417. The criteria used to evaluate the validity and reliability of clinical studies for the purpose of establishing comparative efficacy of drugs include: (a) where analgesics are involved, an appropriate pain model using the subjective response methdology; (b) replication of results; (c) an experienced, unbiased investigator; (d) adequately trained personnel and appropriately instructed subjects; (e) a written protocol; (g) double-blinding; (h) where pain relief is being measured, use of a placebo control; (i) use of appropriate analytical techniques determined in advance; (j) use of a **[101]** recognized level of statistical confidence (the 5% level) to determine the statistical significance of

the observed results; (k) determination of the clinical significance of the test results; and (l) subjecting the study to peer review.

418. Other methods which purport to measure comparative efficacy of analgesic agents, or other techniques which try to assess their comparative efficacy without actual clinical measurement, have not been shown to be sufficiently reliable for the purpose of establishing the comparative efficacy of one agent or product over another.

419. Experts who study the therapetutic performance of analgesics in clinical pain have used several "pain models"; surgical pain, orthopedic pain, post-operative pain, cancer pain, post-partum pain, pain from dental extraction, and headache pain (CX 466, p. 35382).

420. Since pain is a personal perception and subjective in nature, clinical studies of OTC analgesics usually employ the subjective pain response methodology that elicits the subject's report of his or her perception of pain and the degree of pain relief obtained after administration of the drugs under study (Moertel, Tr. 6259; DeKornfeld, Tr. 8390; Feinstein, Tr. 16441; CX 466, pp. 35377, 35444). Objective measures of pain relief, in the strict sense of the term, in the clinical situation are yet to be developed (Feinstein, Tr. 16223).

421. In order to establish the comparative efficacy of drugs, including OTC analgesics, for the relief of mild to moderate pain, at least two well-controlled, separately conducted clinical studies on the drugs in question are required (Moertel, Tr. 6289; Grossman, Tr. 7459, 7466; DeKornfeld, Tr. 8390, 8396–97, 8401; CX 466, pp. 35371, 35444). Replication of results in the hands of separate, competent investigators reduces the likelihood that the results obtained in the original study were due to chance (Moertel, Tr. 6278; Grossman, Tr. 7466; DeKornfeld, Tr. 8390) and avoids the possibility that errors or artifacts in the design or execution of any one study are carried over into the next (DeKornfeld, Tr. 8396–97). As Dr. DeKornfeld testified:

> [Two studies] substantially decrease the likelihood of the one study being inaccurate. Statistically two studies showing the same thing are substantially more meaningful than a single study in an area where there is some question as to difficulty of the methodology (DeKornfeld, Tr. 8396).

422. A threshold requirement for an adequate and well-controlled study is an experienced investigator (Moertel, Tr. 6257; DeKornfeld, Tr. 8394). Moreover, the motivation of an investigator is a possible source of bias, and it is therefore [102] important to ensure that the investigator is truly independent (Moertel, Tr. 6482–83).

423. Where nurses or other persons are used to administer treatments, and to observe and record the subjective responses of patients under study, it is important that they be trained and experienced in

order to guard against intended or unintended distortion of the information provided by patients (DeKornfeld, Tr. 8403).

424. In out-patient clinical studies, where patients are ambulatory and record their own responses to treatment at their homes, due care must be exercised in order to insure that a trained technician accurately compiles the data and the patients themselves are carefully instructed to properly record their responses (Moertel, Tr. 6259–60).

425. A written protocol which sets forth in sufficient detail and in advance the objectives of the study and how those objectives are to be achieved is an important element of a well-controlled clinical study (Moertel, Tr. 6264; DeKornfeld, Tr. 8393). Such a protocol should cover not only the main features of study design, but also a plan for analysis (Moertel, Tr. 6275; DeKornfeld, Tr. 8393). Adherence to the protocol in both its design and analytic features provides a reader of the study with an additional means to judge whether there was an opportunity for uncontrolled bias to enter into the conduct of the study (Moertel, Tr. 6273).

426. The clinical study must employ a pain model that is appropriate for the proposition sought to be tested in the study (Moertel, Tr. 6260). In general, the best pain model is the type(s) of pain for which use of the drug is intended or for which a specific claim of efficacy may be made (DeKornfeld, Tr. 8395). Where a claim of comparative efficacy is made for ordinary headache pain, at least one of the well-controlled studies required to establish such claim should be in ordinary headache pain (DeKornfeld, Tr. 8395, 8444). The need for at least one study which tests the specific type of pain for which a claim is made becomes acute where the product involved is a combination of ingredients, which may act differently in different types of headaches or pain.

427. In a well-controlled clinical study, it is essential that subjects be randomly assigned to the various treatment groups in the study (Moertel, Tr. 6205–06; Grossman, Tr. 7490; Rickels, Tr. 7935; DeKornfeld, Tr. 8393; Feinstein, Tr. 16219, 16465; CX 466, p. 35444). Randomization is necessary to balance out the numerous variables, not only in the subject population but also in the design and conduct of the study itself, that cannot be identified and controlled directly by the investigator (Moertel, Tr. 6265). Randomization is the prerequisite for concluding that the uncontrollable variation inherent in all **[103]** research is fairly balanced across the treatment groups within determinable limits. Unless a clinical study is properly randomized, the validity of that study is questionable and all analyses of its results are compromised.

428. A technique to help assure that important, identifiable variables are balanced fairly across treatment groups is to stratify all

subjects according to such variables (*e.g.,* level of initial or base-line pain) and then randomly assign subjects within each stratum to the various treatment groups. Stratification makes it more likely that the critical variables will be distributed fairly equally in all treatment groups (Moertel, Tr. 6267).

429. An absolute prerequisite of any well-controlled clinical study, particularly in the area of mild analgesic drugs for the relief of mild pain, is double-blinding. That is, neither the test subject nor the investigator should be able to detect the treatment being administered (Moertel, Tr. 6265; Grossman, Tr. 7490–91; DeKornfeld, Tr. 8393, 8399; Feinstein, Tr. 16223; CX 466, p. 35444). Responses to pain relievers can be significantly affected by subjects' pre-existing beliefs and expectations (Moertel, Tr. 6265). Moreover, the conscious or unconscious biases of the investigator, nurse observers, the subjects and others involved in the conduct of the study can exert an influence that distorts the action of the actual treatments administered (DeKornfeld, Tr. 8398). Double-blinding effectively controls the expectations and beliefs of subjects and the biases and influences of those conducting the study, by assuring that these extraneous influences do not distort the results obtained with any given treatment (Moertel, Tr. 6265). To achieve an adequately double-blinded study, it is essential that the treatments look the same, taste the same and appear identical in all respects so that the subjects in one treatment group will not be prompted to expect something different from subjects in another and so that investigators will have no clue as to which treatment they are administering (Moertel, Tr. 6265; Feinstein, Tr. 16223).

430. Whenever possible, a well-controlled study comparing the efficacy of one drug against that of another, particularly mild analgesics, should include a placebo control (Moertel, Tr. 6268; DeKornfeld, Tr. 8393, 8399, 8482; CX 466, pp. 35372, 35444–45). The placebo, a pharmacologically inert substance, acts as a separate treatment in the study, and it serves as a built-in measure of the sensitivity of the study and an analytical tool to aid in the analysis of the results (Moertel, Tr. 6268; Rickels, Tr. 7938–39; DeKornfeld, Tr. 8399; Feinstein, Tr. 16221). Unless the results of a study demonstrate its ability to distinguish a standard analgesic compound—such as aspirin—from placebo, one can...t be certain that the study was sufficiently sensitive to detect differences between the standard and test compounds under study, even if such differences [**104**] in fact existed (DeKornfeld, Tr. 8482, 8484–85). Similarly, in the absence of a placebo control, the failure to find a difference between the treatments under study may be due to insensitivity of the study methodology rather than to the fact that no difference exists between the treatments (Moertel, Tr. 6344).

431. The statistical techniques to be employed in analyzing the results of clinical trials should be set out in advance and be appropriate to the design and purpose of the study (Moertel, Tr. 6275; Rickels, Tr. 7935; DeKornfeld, Tr. 8393–94, 8400). Deciding upon the statistical analysis in advance guards against the investigator "peeking" at the data and terminating a study prematurely when a desired result has been reached or choosing post facto to analyze a particular segment of the study that shows a desired result (Moertel, Tr. 6274, 6345). Failure to set forth statistical procedures in advance opens the door to a bias into the analysis (DeKornfeld, Tr. 8400) and raises a spectre of "data massaging" that may destroy the validity of the analysis (Moertel, Tr. 6346).

432. When a clinical study is designed for the purpose of determining whether two treatments are significantly different from each other a method must be provided with which to judge whether any observed differences may be due to chance or simple random variations in the data generated rather than to real differences in the effects of the treatments (Moertel, Tr. 6273). When the observed differences are shown through appropriate statistical analyses' to be significant at or beyond the 95% level, scientists generally, accept those differences as real and not being due to mere chance (Moertel, Tr. 6273; DeKornfeld, Tr. 8400). The scientific community will not accept, for the purpose of establishing a scientific or medical proposition, a greater-than-5% (or one in twenty) likelihood that the differences observed in a study are due to chance (Moertel, Tr. 6273; DeKornfeld, Tr. 8400). The 95% confidence level as a measure of statistical significance (sometimes expressed as $P < .05$) is a commonly accepted standard for testing the statistical significance of results in biomedical sciences, including the scientific literature (Moertel, Tr. 6273; DeKornfeld, Tr. 8400). For example, respondent's witness, Dr. Horner, in his statistical analysis of the FDA *in vitro* aspirin test data in RX 415, used the .05% confidence limits as his outermost measure of statistical significance (RX 415).

433. When a determination is made that an observed difference between two treatments is statistically significant at or beyond the 95% level, clinicians address the separate question of whether such statistically significant differences have clinical importance (Moertel, Tr. 6253; Feinstein, Tr. 16428). Differences, though statistically significant, may be so minor and insignificant clinically as to have no substantive impact upon therapeutic considerations (Moertel, Tr. 6253). **[105]**

434. Selection of a specific and objective standard of clinical importance—as opposed to the statistical significance—of differences observed between drugs is an important decision which investigators

must make before starting a clinical trial (Moertel, Tr. 6271). Unless a difference is statistically significant at or beyond the 95% level, it cannot be clinically important (Moertel, Tr. 6588). However, it is possible to demonstrate the statistical significance (at the 95% level) of even minute differences by expanding the test population sufficiently (Moertel, Tr. 6253; Feinstein, Tr. 16326, 16429–34). It is therefore generally recognized that in clinical trials statistical significance alone does not provide the basis for a conclusion about the therapeutic significance of those differences, which is ultimately a clinical question (Feinstein, Tr. 16335, 16428–29). Thus, differences may be statistically significant but not clinically significant (Moertel, Tr. 6253).

435. Publication of a clinical study in a reputable journal and the accompanying process of peer review adds further elements of reliability and confidence to a study (Moertel, Tr. 6280; DeKornfeld, Tr. 8394). It allows an opportunity for other experts in the field familiar with research methodology to see whether the study was properly designed and conducted, whether results have been properly interpreted and whether a protocol has been properly followed (Moertel, Tr. 6280). One of the important criteria used in coming to a conclusion about the validity and reliability of a study is whether it is published in a reputable, peer reviewed journal and whether, thereafter, it meets with the acceptance of other scientists in the field (Moertel, Tr. 6280).

436. On the other hand, a practicing physician may choose to try on a given patient a therapeutic agent whose superior efficacy has not been established in the manner discussed above. For example, a clinician may try buffered aspirin on a patient who had complained of gastric discomfort after taking plain aspirin simply on the basis of some historical or clinical data indicating that some subjects sometimes appeared to have suffered somewhat less gastric discomfort from buffered aspirin. If the patient under discussion does experience less gastric discomfort from buffered aspirin, the clinicial will thereafter prefer buffered aspirin over plain aspirin for that patient. However, this is essentially a part of the trial-and-error process inherent in clinical practice and is an incidence of the well known fact of human variability. In this case, the difference between plain and buffered aspirin had "clinical significance" for the physician and the patient involved. This is not to say, however, that the evidence at hand is sufficient to support a comparative therapeutic proposition which the medical scientific community will accept as established. Thus, [106] clinical preference that clinicians may make on the basis of historical survey data or anecdotal clinical experience (in the absence of controlled clinical trials) is distinct from the evaluation of clinical significance of a statistically significant difference found be-

tween drugs. The former is a clinical judgment that a practicing physician must make in his daily practice on the basis of available evidence; the latter is a clinical judgment he makes of an agent whose efficacy or comparative efficacy has been statistically demonstrated through controlled trials.

2. The Claim That Bayer Aspirin is Therapeutically Superior to All Other Brands of Aspirin Lacked A Reasonable Basis and It is Reasonable to Require Well-Controlled Clinical Trials to Support Claims of Therapeutic Superiority For Bayer Aspirin.

437. Clinical trial methdology is not new. Dr. A. Bradford Hill, a British medical statistician, was instrumental in bringing about the recognition of clinical trials before 1950. Since the time of Hill, clinical trials have been recognized as the only reliable method for demonstrating the efficacy of drugs. The importance of clinical trials for this purpose is now widely recognized (Moertel, Tr. 6285; Grossman, Tr. 7462–66; 21 C.F.R. 330.10 (a)(4)). The use of randomized double-blind, controlled clinical trials dates back to the 1940's. During the early 1950's, Hill summarized the procedures and rationale for controlled clinical trials for the purpose of making therapeutic conclusions regarding drugs. During the same decade, Beecher, Houde and Modell elaborated on clinical study requirements in the context of analgesic studies. And in 1965, Dr. William Beaver summarized the procedures for conducting clinical trials of mild analgesics in a historic review article (Moertel, Tr. 6288). In recognition of the significance of such clinical trials, interest has grown in recent years in perfecting the methodology (Grossman, Tr. 7466; DeKornfeld, Tr. 8393, 8406; Feinstein, Tr. 16233, 16255, 16425, 16470–71).

438. Respondent's witness, Dr. Feinstein, testified on the need for incorporating what he refers to as "soft data" into the evaluation of medication. Soft data measures symptoms such as pain or digestive distress whereas hard data measures blood salicylate levels or brain wave pattern or pharmaceutical characteristics of drugs (Feinstein, Tr. 16444–49). He agreed that if the purpose of drug is to relieve a subjective symptom such as pain, it is of critical importance to directly measure the pain itself in people (Feinstein, Tr. 16441).

439. Dr. Raymond Houde, in discussing clinical measurement of pain in 1965 wrote:

> In spite of the relative convenience and more rigorous controls which can be applied in the [107] laboratory, the control drug study in the clinical setting is now more than ever the crucial test of any new analgesic. This is true for several reasons. Most obviously, the only conclusive proof of the value of a drug in the therapy of a disease or the alleviation of a symptom lies in successful therapeutic trials in patients with that particular disease or symptom.

Indeed, an increasing number of investigators in the past decade or so have been able to show that controlled clinical experimentation can provide results which are reproducible and valid in the sense that they have held up well under the test of subsequent and more extensive clinical experience (RX 250–DeStevens; Goldstein, Tr. 15756).

This view was reiterated by complaint counsel's expert witnesses. They testified that the techniques for measuring differences in performance of mild analgesics are available and if used properly can lead to clinically significant results (Moertel, Tr. 6288; Grossman, Tr. 7462; DeKornfeld, Tr. 8460).

440. Well-controlled clinical trials need not be prohibitively expensive. Dr. Moertel, long experienced in the conduct of clinical trials of analgesics, noted that suitable patient populations are available at large medical centers for such trials. Thus, the only costs which need be incurred are those associated with the preparation of the drug, proper coding and cost of analysis of results (Moertel, Tr. 6288). Moreover, correspondence between Sterling and Food and Drug Research Laboratory (FDRL) in 1964 indicated that the costs of running the Cope clinicals was low—approximately $25–$27 per subject (RX 237F).

441. The concept of therapeutic superiority includes considerations of both safety and efficacy (Grossman, Tr. 7459). Where a side effect has a high enough incidence in the population, such as dyspepsia resulting from aspirin, clinical trials are appropriate to evaluate the relative safety of two mild analgesics (Grossman, Tr. 7459–60). Preclinical studies in animals on side effects can be valuable in finding areas of possible clinical side effects, but just as efficacy must be tested in appropriate studies in human patients, so must side effects be determined on the basis of human studies (Grossman, Tr. 7460).

442. As Sterling was well aware in 1971, both the medical and pharmacy professions universally believed that all aspirins were the same (CX 329). Presumably that belief was based on a [108] lack of evidence of clinically significant differences between different brands of aspirin.

443. The record shows that before and during the time Sterling made therapeutic superiority claims for Bayer, Sterling was aware of and familiar with clinical trial methodology and its application to comparative analgesiology. Sterling in fact demanded that its competitors meet this standard as substantiation for their superiority claims. Also, when Glenbrook Laboratories first contracted with FDRL for a series of comparative clinical tests of its combination products, Cope and Vanquish, in the early 1960's, FDRL advised Dr. Painter of Sterling in 1963 of the following, in a section entitled "Protocol—Evaluation of an Analgesic-Sedative Preparation":

Because FDA and FTC are refusing to recognize the validity of uncontrolled studies, particularly with drugs intended entirely for relief of symptoms, all such studies should be carried out double blind against a standard . . . If needed to substantiate an NDA or to strengthen claims for the FTC, more than one could be placed (RX 237C–D).

444. Sterling recognized the need for clinical trials as early as 1953 when it petitioned the FTC for issuance of a complaint against its competitor Bristol-Myers for unsubstantiated advertising claims. At that time Sterling said:

Three separate, distinct and independent studies have been made of this question, and to as great an extent as practicable, the double blind cross-over technique was used. All these tests were clinical tests which went to the heart of the matter by learning from the patient directly how quickly and how completely his pain was relieved. There is no known scientific method superior to this method. (CX 371Z001).

445. This belief in the need for clinicals to establish a claim of superiority is also reflected in more recent Sterling internal documents. Sterling's then advertising agency complained in 1970 to the television networks about false, unsubstantiated claims for Excedrin by its competitor Bristol-Myers. In criticizing a study supposedly supporting Excedrin's superiority claims, the agency posed the following questions, noting that "answers . . . ought clearly to be provided before the study can be evaluated as the basis for advertising claims" (CX 347C):

1. Did the study design utilize the customary "double blind" technique? If not, what steps **[109]** were taken to insure that the results would not be biased by the questioner? (This is highly important in view of the subjective questioning technique being tested in this research).

2. Since a "cross-over" technique apparently was not utilized, what controls were employed to insure that the patient samples were properly matched on all important variables; e.g., age, type of pain, length of time since delivery, etc.?

3. Similarly, what means were employed to insure that the individual patient samples were of sufficient size for meaningful analysis? (Instances in the charted results show, for example, that at certain intervals *two* aspirin tablets proved to be as efficacious as *four* Excedrin tablets and, for that matter, that two Excedrin tablets are *more* effective than four Excedrin tablets). (CX 347C).

446. Another indication of Sterling's recognition of the feasibility and reliability of clinical studies comparing the safety and efficacy of analgesics was its reliance on the results of the Lasagna-DeKornfeld study (RX 450) published in *Journal of the American Medical Association* ("JAMA") in 1962. Sterling disseminated Bayer advertisements citing the results of the study (*FTC v. Sterling Drug, Inc.*, 215 F.Supp. 327 (S.D.N.Y. 1963), *aff'd*, 317 F.2d 669 (2d Cir. 1963).

447. More recently, in 1974, Dr. Monroe Trout, Senior Vice Presi-

dent and Director of Medical Affairs for Sterling Drug, appeared before FDA's Panel on OTC Internal Analgesics. Requesting that the Panel set down appropriate rules govening variances from the standard 325 mg dose of aspirin, he suggested:

> . . . that OTC analgesic products containing aspirin, with or without additional ingredients . . . include on their label [a disclosure that the product] is not superior in safety, effectiveness, speed of relief, or incidence of side effects to two 5 grain tablets or 650 mg of aspirin, *unless the superiority claimed or implied by such variance is adequately established by well-controlled studies of pain relief, anti-pyresis, anti-inflammatory, or side effects.* (CX 456M) [emphasis added]

448. And in 1976, Dr. George Goldstein, then Vice-President and Medical Director of Glenbrook Laboratories division of [110] Sterling, submitted comments to the OTC Analgesics Panel on its Draft Report. The Panel had classified buffered aspirin claims in Category III, which includes those claims for which available data were found to be insufficient to permit final classification. Dr. Goldstein urged that claims of superiority based on increased rate of absorption, decreased incidence of gastric distress or the inference of greater safety for buffered aspirin products be placed in Category II, requiring sufficient clinical demonstration before asserting the claim. As he explained ". . . getting into the bloodstream faster is only important if one has painful blood." (CX 574C–D). Thus, Dr. Goldstein reasserted Sterling's position held over the past 25 years—that nonclinical data, even blood level studies, are not sufficient to support claims of therapeutic superiority in light of available clinical trial methodology.

449. The FDA Monograph Panel on OTC Internal Analgesics, Antipyretic and Antirheumatic Products (or FDA Analgesic Panel), has incorporated these principles and requirements for well-controlled clinical studies into its Final Report published in July 1977 (CX 466, pp. 35371, 35444–45). Since the mid-1960's the FDA, in regulations promulgated pursuant to the 1962 Food, Drug & Cosmetics Act, has codified many of these principles into its regulations mandating the need for "substantial evidence" to support efficacy claims for new drugs (21 C.F.R. 314.111(a)(5)(ii)(a) through (c); 330.10(a)(4)). However, the record shows that during the period from 1963 through 1971, there was no FDA requirement with respect to currently marketed OTC drug products (such as aspirin products) that their efficacy be demonstrated through well-controlled clinical trials.

450. Apart from the fact that the medical scientific community has long recognized and accepted the need for clinical demonstration for drawing therapeutic conclusions, it is fair and reasonable, given respondent's familiarity with the standard and past recognition of its

feasibility, that it should be held to the same standard in the instant proceeding.

451. During the trial, however, Sterling vigorously advanced a position which would apply different standards of substantiation to therapeutic superiority claims for buffered or combination aspirin products on the one hand, and similar claims for plain 5-grain aspirin on the other. With respect to the former, Sterling would insist on well-controlled clinical studies. As to the latter, including therapeutic superiority claims for Bayer Aspirin and Bayer Children's Aspirin, Sterling would accept evidence of pharmaceutical or physicochemical differences between brands as adequate substantiation in the absence of well-controlled clinical studies. Indeed, Sterling contended that the FDA has modified its requirements for well-controlled clinicals to demonstrate efficacy and safety of drugs to accept or prefer nonclinical data, such as bioavailability [**111**] data (blood level data and dissolution/absorption data) in similar cases involving pharmaceutical equivalents such as plain 5-grain aspirin tablets. *See* RPF 7.1–7.459, 7.472–7.665, 7.696–7.754, 7.755–7.785, 7.786–782.

452. I have carefully reviewed the record as a whole and find Sterling's contentions unpersuasive. *First,* the record is clear that a proposition of therapeutic superiority of one brand of plain 5-grain aspirin over another correctly formulated brand based solely on physicochemical differences remains a hypothesis to be clinically tested even though the hypothesis may appear rational and plausible in terms of pharmaceutical and pharmacological principles. *Second,* even in terms of pharmaceutical and pharmacological principles, the inference to be drawn from physicochemical difference is often a matter of degree. The record also indicates not only that some physicochemical characteristics of plain aspirin tablets, such as dissolution, may have a greater bearing on the therapeutic performance of the tablet than other characteristics, but also that some of the desirable characteristics are mutually antagonistic, in the sense that one can be enhanced only at the expense of some of the others. Even in cases where statistically significant differences in some physicochemical characteristics are shown, the central question of whether such differences in themselves are sufficient to make a significant therapeutic impact *in actual use* can be resolved only through well-controlled clinical trials. The oft-heard assertion that, other things being equal, a plain 5-grain aspirin brand which is better than other brands in terms of one or more physicochemical characteristics is preferable is begging the question. *Third,* the various physicochemical studies of plain 5-grain tablets Sterling relied on at trial are equivocal or suggestive only or unreliable because of serious deficiencies in the design, execution and/or analysis of the studies or failure to show statistical signifi-

cance or because of serious doubts regarding the therapeutic significance of the observed differences (*e.g.*, blood level studies as a basis for comparative efficacy claims of aspirin products).

453. Since the early 1960's there has been little dispute in the biomedical scientific community that the efficacy and safety of drugs must be demonstrated by well-controlled clinical studies, including appropriate replication. The record shows that Sterling has subscribed to this view. In recent years, a vocal dissent from that position has emerged, mainly from those who believe that the strict FDA requirements are exacting excessive costs in terms of research and economic resources and speedy introduction of safe and effective new drugs. They urge that other less costly alternatives must be accepted. However, the dissent represents a minority view in the United States. It is found that the need for clinical demonstration becomes more acute when the issue is of comparative efficacy or safety. **[112]**

454. There appears to be a paucity of literature regarding the requirement of well-controlled clinical trials with respect to pharmaceutically equivalent drugs, such as plain 5-grain aspirin tablets. In the administrative law judge's view, a common sense explanation of this fact is that scientists generally believe, as a basic proposition, that pharmaceutical equivalents are therapeutic equivalents until the contrary is shown to be the case with respect to any given product. Thus, those who claim therapeutic superiority of one product over other pharmaceutical equivalents (for example, plain 5-grain aspirin tablets) must demonstrate the therapeutic superiority of that product through well-controlled clinical tests. Until this has been done, the superiority claim remains unsubstantiated. Complaint counsel's expert witnesses supported this view.

455. There is little dispute in the record that drug product quality is important because it can significantly affect the drug's therapeutic performance. It is the administrative law judge's view that the improvement of drug quality should be encouraged as a matter of public policy not only for this reason but also for its own sake.

456. On the other hand, those who claim superiority in terms of drug product quality (pharmaceutical superiority) must have and rely on adequate substantiation. In the case of plain 5-grain aspirins, such substantiation must include a scientifically and statistically sound comparative study of a representative sample of plain 5-grain aspirin brands which shows statistically significant differences that are also clinically significant.

457. A cornerstone of Sterling's evidence in support of its position that a claim of therapeutic superiority of Bayer Aspirin over other brands of plain 5-grain aspirin does not require clinical demonstration is the expert testimony of Dr. Alvan R. Feinstein, now Professor

of Medicine and Epidemiology at Yale and an expert in the history and use of well-controlled clinical trials as a method for evaluating the clinical effectiveness of drugs, and a number of published articles on the subject of controlled clinical trials Dr. Feinstein discussed during his testimony.

458. Although Dr. Feinstein's position appeared somewhat ambivalent, the conclusion of his testimony was that well-controlled clinical trials are the best way of establishing a therapeutic proposition. However, in Dr. Feinstein's view, that requirement has turned into an inflexible dogma and there is a need to develop alternative ways of evaluating therapeutic conclusions in cases where randomized controlled clinical trials are not feasible for well-founded and cogent reasons. Neither Dr. Feinstein nor any of the published literature he discussed suggested that controlled clinical trials should no longer be [113] required or that they be abolished for the purpose of establishing the comparative efficacy of one drug product over another. As a matter of fact, the most recent article Dr. Feinstein authored on this subject, "Editorial: Should Placebo-Controlled Trials Be Abolished?", *Eur. J. Clin. Pharmacol.* 17:1–4 (1980) (RPF 2.13(h)) is a succinct exposition of the fundamental rationale underlying randomized controlled clinicals and is a cogent defense of that requirement except for a few well-defined situations, which does not include the situation involved in this case.

459. Dr. Feinstein also testified that, where feasible, randomized controlled clinical trials are the preferred method of measuring therapeutic superiority, particularly where the therapeutic response is a primarily subjective entity such as pain (Feinstein, Tr. 16223). He further explained that "in making a therapeutic decision I would have a hierarchy of evidence. And in that hierarchy, direct evidence in clinical usage would have a higher position than physicochemical kinds of evidence" (Feinstein, Tr. 16380).

460. Even in clinical usage as identified by Dr. Feinstein, there is some gap in patients' pain responses and blood level data. Although a threshhold blood level must be achieved before analgesic action begins, that level is subject to a wide variation among individuals. It is also well recognized that a correlation between blood levels and the onset, duration, or intensity of pain relief has yet to be shown. However, there is an even wider gap between actual clinical effect and the drug's physicochemical characteristics (such as rate of dissolution, disintegration, amount of impurities, particle size, aspirin content and tablet color). In fact, any such relationship remains hypothetical until it is demonstrated through clinical trials.

461. On the other hand, Sterling's pharmaceutical expert witnesses were more emphatic in their support of the proposition that physico-

chemical data is sufficient to support a conclusion of comparative efficacy of plain 5-grain aspirin brands. They include Drs. G.S. Banker and C. Rhodes, both well recognized pharmaceutical scientists. They testified to their own views and also discussed a number of pharmaceutical studies in evidence as well as a large amount of published material in the field of pharmaceutical sciences.

462. The burden of the testimony of Drs. Banker and Rhodes was that it was reasonable to make a comparative "therapeutic judgment" regarding different formulations of the same drug (such as plain 5-grain aspirin) solely on the basis of the differences in the various physicochemical characteristics among brands. They suggested that controlled clinical trials are superfluous and unnecessary in cases where, as in the case of plain 5-grain aspirins, physicochemical evidence alone can [114] provide an adequate basis for making a comparative "therapeutic judgment."

463. Sterling also presented the testimony of a few clinical pharmacologists who are also medical specialists. Essentially, they testified that the physicochemical data and the bioavailability data in evidence, together with other medical scientific literature they discussed at trial, provided a sufficient basis for making a comparative "therapeutic judgment" regarding Bayer Aspirin and other aspirin brands. Such expert witnesses include Dr. I.E. Danhof (a physiologist with special interest in gastroenterology) and Dr. W.C. Fields (a neurologist). Several company witnesses also testified in support of Sterling's position discussed in the preceding paragraphs.

464. In its proposed findings and post-trial brief, Sterling elaborated upon its "policy" and argued essentially that randomized controlled clinical trials, while appropriate for comparative efficacy or safety claims involving combination or buffered aspirin products, are not appropriate for comparative therapeutic claims involving different brands of plain 5-grain aspirin (RPF 7.811–7.825; RB 211–229).

465. On the other hand, complaint counsel's expert witnesses, who are eminently qualified in the field of analgesic testing, testified that while pharmaceutical and pharmacological principles, together with clinical observations, can suggest an hypothesis involving a comparative therapeutic proposition, it remains an hypothesis until it is verified and confirmed by well-controlled clinical studies. I find this view more logical, consistent and persuasive than the view advanced by respondent's experts. Although the FDA-OTC Analgesic Panel did not deal with comparative efficacy of different brands of plain 5-grain aspirin, it adopted a similar approach with respect to the question of buffered aspirin products. Faced with a substantial amount of literature and expert presentation suggesting the benefits of buffered aspirins, the Panel concluded that the proposition remains unproven

until conclusively demonstrated by well-controlled clinical studies and they disallowed label claims of greater safety of buffered aspirin tablets. That approach is applicable here with respect to alleged therapeutic superiority of Bayer over other USP aspirin tablets based on physicochemical differences alone. *See* CX 466 at 35469–70, 35480.

466. Robert John, former Medical Director of Glenbrook Laboratories, testified that there is an expectation in the scientific community that where a claim for therapeutic superiority is made it will be supported by clinical evidence [115] (John, Tr. 5661). He believed that claims for therapeutic superiority had to be supported by evidence showing a statistically significant clinical difference between drug products (John, Tr. 5570, 5661). Because there was no such evidence, he would have withheld approval of any advertising claim for therapeutic superiority for Bayer Aspirin (John, Tr. 5586–87). His understanding of the Bayer advertisements he reviewed while at Bayer was that they did not contain any therapeutic superiority claims and contained only pharmaceutical quality claims (John, Tr. 5586–87).

467. Various attempts to measure the simple and comparative efficacy of mild analgesics other than well-controlled clinical trials have not been shown sufficiently reliable to establish simple or comparative efficacy in humans.

468. The fact that an OTC internal analgesic product may contain a combination of ingredients, or more ingredients than another OTC analgesic product, is not acceptable evidence that it is more effective (CX 456M). In order to conclude that one analgesic—even with more ingredients—is more effective than another, one needs well-controlled clinical studies.

469. No correlation has yet been established between the amount of drug appearing in the bloodstream at some time point and the degree of pain relief afforded by an analgesic (CX 678, admission 722). Therefore, "blood level" studies, *i.e.,* studies that simply examine the amount of a drug in the bloodstream at various time intervals following ingestion of a product, are not a reliable basis for predicting comparative analgesic performance. Thus, studies which are limited to a showing that one analgesic preparation is absorbed more rapidly than another cannot support conclusions regarding the onset, duration or intensity of analgesic action of drugs. *See* F. 502, *infra.*

470. Studies employing experimental pain, *i.e.,* pain induced in humans in the laboratory, are insufficiently reliable for use in establishing the comparative efficacy of OTC internal analgesics. Experimental pain studies have failed to predict with any consistency the clinical performance of analgesic drugs, particularly those used for OTC medication (CX 466, p. 35444).

471. Consumers' perceptions are not reliable evidence to establish

the efficacy or comparative efficacy of OTC internal analgesics because consumers cannot "evaluate" for themselves **[116]** the simple or comparative pharmacologic efficacy of drugs (DeKornfeld, Tr. 8421). The inability to "evaluate" refers to consumers' inability to distinguish the pharmacologic contribution supplied by a drug from a host of factors that are extraneous to the drug's true pharmacologic effect.

472. Expectations concerning the performance of drugs are an important extraneous factor and they play a powerful role in influencing the response of test subjects to drugs. Such expectations are directly affected by other extraneous factors such as the subject's general disposition, past experience with the drug, relationship with the physician or nurse administering treatment, the size, shape and taste of the pill taken and advertising the subject has seen (Feinstein, Tr. 16289).

473. Consumers on an unblinded basis cannot differentiate between a true pharmacologic response and a response due to extraneous factors, such as suggestions or expectations, that surround the taking of the drug. The influence of extraneous factors is often sufficient to cause even blinded subjects in a controlled test to report pain relief in the absence of any pharmacologic action of a drug (Moertel, Tr. 6544; DeKornfeld, Tr. 8405). Frequently described as the "placebo effect," these nonspecific factors alone are typically reported in scientific literature as producing pain relief in over 30–50% of subjects involved in controlled analgesic studies (Moertel, Tr. 6544; Feinstein, Tr. 16322). Furthermore, anyone on any occasion can be a "placebo responder" (DeKornfeld, Tr. 8405). Expectations and similar factors, and hence the "placebo effect," cannot be entirely eliminated from any situation where a human suffers pain. However, well-controlled clinical studies can control such expectations by ensuring that the treatments under study are equally affected by them (F. 427–430, *supra*).

474. It has not been established that Bayer is superior to any other plain 5-grain aspirin in terms of pain relief.

475. RX 450, "A Comparative Study of Five Proprietary Analgesic Compounds" ("Lasagna-DeKornfeld Study") was conducted by Drs. Louis Lasagna and Thomas DeKornfeld with Todd Frazier, a biostatistician. The purpose of the study, undertaken at the request of the FTC, was to determine if superior pain relief claims by any of the manufacturers of ITC internal analgesic products could be substantiated by clinical evidence (DeKornfeld, Tr. 8332).

476. Though Sterling's expert witnesses criticized the methodology applied by Lasagna-DeKornfeld in light of present day techniques, the record shows that, at the time it was published, respondent was not

only aware of the study (John, [117] Tr. 5546–47) but found it reliable. In fact, respondent relied upon it in advertising to support certain claims (CX 678, admission 713), and cited the study in formal complaints made to the Federal Trade Commission against certain advertisements of its competitors (CX 678, admission 714).

477. The Lasagna-DeKornfeld study was designed to be randomized, placebo controlled and double-blinded. In this cross-over study, all the patients were given all the treatments. Its purpose was to compare the efficacy of five over-the-counter internal analgesics in relieving post-partum pain (DeKornfeld, Tr. 8333). Of the products tested, Bayer and St. Joseph's were plain 5-grain aspirins, Excedrin and Anacin were combination analgesics containing aspirin, phenacetin and caffeine, and Bufferin was aspirin plus buffers (DeKornfeld, Tr. 8333).

478. The study was published in a 1962 issue of the *Journal of the American Medical Association,* a respected medical journal, and was subjected to peer review prior to publication (DeKornfeld, Tr. 8351). The methodology used in the Lasagna-DeKornfeld study was fairly conventional for 1962 (Feinstein, Tr. 16388) when the study was published.

479. At the time the Lasagna-DeKornfeld study was done, there was no regulatory requirement that the raw data be retained. Such requirements were imposed as a result of legislation enacted in 1962 (DeKornfeld, Tr. 8351). The editors of the journal in which the study was published were provided with the underlying data prior to publication (DeKornfeld, Tr. 8356). However, the underlying data is no longer available (DeKornfeld, Tr. 8351).

480. Post-partum pain is one of a number of pain models generally accepted in testing mild analgesic agents (DeKornfeld, Tr. 8370). Dr. DeKornfeld agreed that patients with post partum pain might be suffering episiotomy pain or uterine cramp pain. His study did not stratify for these two different types of pain (DeKornfeld, Tr. 8373). However, the different groups were examined afterward to assure an even distribution of variables which might have affected scoring the performance of the drugs and concluded that stratification in fact had occurred as a result of simple randomization (Tr. 8445–48).

481. A potential problem in cross-over pain studies is the possibility that a patient's pain might decrease by the time a second or subsequent dose is administered. Because of its nature, post-partum pain tends to be steadier for a longer period of time than other types of pain (DeKornfeld, Tr. 8478), thereby minimizing this problem. [118]

482. The Lasagna-DeKornfeld study was designed to be double-blinded, but because its purpose was to compare brands of aspirin and aspirin compounds in their commercially available state, the drugs did not all look alike at the time of administration (DeKornfeld, Tr.

8374). The patients were given aluminum foil packets containing the different brands and every attempt was made to assure that the patients did not see what they were taking. Patients were instructed not to look at the medication, and either Dr. DeKornfeld or one of his associates was physically present when all medication was administered to guard against the patients seeing or handling the drugs given to them (DeKornfeld, Tr. 8375; CX 450B). Even though the investigator who supervised the administration of the medication did not know what particular drug was administered to any patient, the interviewing of patients and the recording of their subjective responses to questions about pain relief was never done by the one who had administered the drug (DeKornfeld, Tr. 8377).

483. A random number table was used to assign patients to different treatment groups (DeKornfeld, Tr. 8453; CX 450B).

484. The sequence in which a series of drug treatments is administered may cause the drugs to perform differently. Such "order effects" were discovered in the 1960's by a group in New York led by Drs. Kantor and Sunshine (DeKornfeld, Tr. 8477). They determined that such effects can be significant in cross-over studies where each participant receives each of the tested drugs and that such effects could be eliminated by doing a "first dose" analysis. Data from the first dose, by definition, could not be influenced by the effects or the order of any subsequent treatments. Having been designed and executed prior to the discovery of order effects, the Lasagna-DeKornfeld study did not include a first-dose-only analysis (DeKornfeld, Tr. 8477).

485. In RX 450 pain relief scores were recorded at intervals of 15, 30, 45, 60, 120, 180 and 240 minutes after administration of drugs (RX 450B). As between the two 5-grain aspirin tablets tested in the study (St. Joseph's and Bayer), mean pain relief scores reflected no statistically significant difference for any of the time intervals (Table 1, RX 450B). In testimony about the results of the study, both Dr. DeKornfeld and Dr. Feinstein found the table confusing to read (DeKornfeld, Tr. 8503–04; Feinstein, Tr. 16405). Each concluded upon first review that the mean pain relief score for Bayer at 120 minutes was statistically significantly higher than that for St. Joseph's. Upon closer scrutiny, however, Dr. Feinstein stated that he was not quite sure although some of the data presented therein appeared to be "consistent with" an inference of a statistically significant difference. [119]

486. Dr. Feinstein agreed that the study does not show any clinically significant differences in therapeutic effectiveness between the products (Feinstein, Tr. 16397, 16437). A clinical difference is one "large enough to be really impressive" (Feinstein, Tr. 16397). Even assuming that the differences in mean pain relief scores were statistically significant, they would not be "really impressive" enough to

have clinical significance (Feinstein, Tr. 16397). Dr. Feinstein concluded that the study, as a whole, does not show a clinically significant difference in therapeutic effectiveness between Bayer and any other aspirin (Feinstein, Tr. 16437).

487. Although the Lasagna-DeKornfeld study is not free from shortcomings, it nevertheless demonstrates two points: (1) it shows that at the time the study was done, randomized, controlled clinical trials on mild analgesics were feasible and being carried out by respected scientists; and (2) respondent was aware that the results of the study found no clinically or statistically significant differences among the brands tested and respondent relied on those results in its advertising as well as in its formal complaints to the FTC.

488. Furthermore, the essential findings of the study themselves—no clinical difference between Bayer and St. Joseph's—should be accorded some weight in this proceeding. The study was conducted by experts with impeccable qualifications. It was randomized, placebo controlled and double-blinded. Although the double-blind protection was not air-tight, and while additional clinical evidence based on other pain models would be necessary to arrive at firm conclusions, the study offers the only clinical evidence extant which addresses the issue of comparative efficacy between brands of 5-grain aspirin tablets.

489. It has not been established that Bayer is superior in terms of number or severity of side effects to any other aspirin.

490. Clinical trials are appropriate to evaluate the relative safety of mild analgesics. Animal studies on side effects of drugs can be valuable in finding areas of possible side effects in humans, but just as efficacy for pain relief must be tested in appropriate studies in human patients, so must side effects be determined on the basis of human studies (Grossman, Tr. 7459–60).

491. Aspirin is known to cause gastric discomfort or dyspepsia in some individuals who take it at OTC doses (CX 466, p. 35387). Dyspepsia is a subjective response which is not necessarily related to acute gastric erosion (CX 466, p. 35387). The incidence of dyspepsia in the general population **[120]** is estimated to range between 5–10% and the literature contains reports of clinical studies designed to measure the relative incidence of side effects among patients taking different formulations of aspirin. Respondent relies on a number of such studies to support claims of superior gentleness for its combination product, Vanquish.

492. Respondent presented no evidence of controlled clinical trials in which the incidence of side effects resulting from Bayer Aspirin was compared to that of any other brand of aspirin. However, it offered animal studies conducted by Dr. Ivan Danhof in which he

compared the effect of Bayer and other experimental formulations of aspirin on the gastric mucosa of dogs (RX 167; Danhof, Tr. 17377).

493. The purpose of Dr. Danhof's studies, which were carried out for Sterling and remain unpublished (Danhof, Tr. 17237), was to compare the incidence and nature of lesions in the gastric mucosa resulting from application of varying aspirin formulations. Dr. Danhof agreed that these studies did not provide a basis for conclusions about comparative degree of injury caused by Bayer and other aspirins because the comparisons did not involve any other commercial brands of 5-grain aspirin (Danhof, Tr. 17377). There is no indication in the report containing these studies whether the results of the studies or the differences shown were statistically significant (Danhof, Tr. 17373). Moreover, evidence of lesions on the gastric mucosa of a dog does not constitute evidence of clinically important side effects in humans. As Dr. Grossman explained, a lesion is a term for any abnormality found in a tissue and may have no clinical importance. Animal studies are merely the basis for hypotheses and cannot be used to establish a biomedical proposition (Grossman, Tr. 7460).

494. Given the absence of any controlled evidence in humans that Bayer causes side effects less frequently than other aspirin, it has not been established that Bayer is superior to any other aspirin because it results in fewer side effects.

495. It is reasonably clear from the record that no well-controlled clinical evidence exists in support of claims that Bayer Aspirin is therapeutically superior to other aspirin. Sterling also knew that the medical profession and the pharmacy profession universally believed, presumably because of a lack of adequate evidence showing differences, that all aspirin is the same (CX 329J). That view was clearly articulated in 1971 by Glenn Johnston of Glenbrook Laboratories in a position paper on Bayer (CX 678, admissions 132, 134). Therefore the claim that the therapeutic superiority of Bayer Aspirin has been established is false.

496. Because Bayer's therapeutic superiority has not been established according to the criteria recognized and adhered to [121] by qualified experts in the scientific community, the claim for such superiority was made in the face of a substantial question recognized by such experts as to its validity, as alleged in Complaint Paragraph 9.

3. Evidence Other Than Well-Controlled Clinical Studies Do Not Provide a Reasonable Basis For Therapeutic Superiority of One Brand of Plain Five-Grain Aspirin Over Another Brand

497. Various measures of comparative therapeutic performance of different brands of plain, 5-grain aspirin upon which Sterling sought to rely in this proceeding have not been shown to be sufficiently

reliable to provide a reasonable basis for a claim that Bayer Aspirin is therapeutically superior to other brands of plain 5-grain aspirin. They are not accepted by experts in the evaluation of analgesic agents as reasonable evidence of comparative clinical performance. These attempted measures not using controlled clinical trials fall into three categories: animal test data; *in vitro* data, *i.e.,* nonclincal data generated by investigations conducted in laboratory equipment; and human *in vivo* data, *i.e.,* nonclinical data generated by investigations in humans.

498. While expert witnesses called by Sterling addressed these various measures in their testimony, their conclusions that such evidence provides reasonable scientific support for therapeutic superiority claims are not well supported.

499. The *in vivo* data in the record consist of (1) serum salicylate level (or blood level) studies which compare different brands of aspirin tablets in terms of absorption into the bloodstream and (2) gastroscopic tablet disintegration data. There is no dispute that aspirin must be absorbed in order to relieve pain. However, no direct correlation has been sufficiently demonstrated between blood levels and pain relief in the case of aspirin. The gastroscopic comparison of disintegration in human stomach of various brands of aspirin tablets included in the Paul study (RX 168) may be called *in vivo* data. However, as detailed in later Findings, comparative tablet disintegration data do not provide a reliable basis for predicting the comparative therapeutic performance of different brands of plain 5-grain aspirin tablets. Furthermore, the question of whether the nature of an aspirin tablet's dispersion, *i.e.,* breaking up into fine or coarse particles, is directly related to side effects associated with aspirin ingestion remains unsettled.

500. The *in vitro* data in the record include pharmaceutical data comparing different brands of plain 5-grain aspirin in terms of: (1) rate of dissolution; (2) rate of tablet disintegration; (3) aspirin content per tablet; and (4) amount of free salicylic acid ("FSA"), and other impurities such as **[122]** aspirin anhydride ("ASAN"), acetylsalicylsalicylic acid ("ASSA"), and salicylsalicylic acid ("SSA").

Blood Levels

501. Like many drugs, aspirin acts in humans by circulating in the bloodstream (Banker, Tr. 13033, 13045, 13057; Rhodes, Tr. 11539, 11751; CX 466, p. 35374). Therefore, it must be absorbed into the bloodstream before pain relief can occur following ingestion of aspirin (Miller, Tr. 6742; Rhodes, Tr. 11539–87). In order to determine the rate and extent of aspirin absorption into the bloodstream, blood level studies are conducted (John, Tr. 5637). These studies measure the

serum concentration of aspirin in blood samples drawn from human subjects at various time intervals after taking aspirin (John, Tr. 5637).

502. For many drugs, the relationship between the drug's levels in the blood and the drug's clinical effect has been determined (CX 466, p. 35377). However, in the case of aspirin, no direct correlation has been demonstrated between the amount of aspirin appearing in the bloodstream at any time and the onset, intensity, or duration of pain relief afforded by aspirin. This fact has been attested to by expert witnesses in this proceeding (Moertel, Tr. 6290–91; O. Miller, Tr. 6740; Grossman, Tr. 7577; DeKornfeld, Tr. 8408–11, 8414; Banker, Tr. 12940, 12999, 13045, and 13057; Feinstein, Tr. 16479, 16481–82; Danhof, Tr. 17269). That this view is widely shared by the scientific community is evidenced by: (1) the report of the FDA Panel on OTC Internal Analgesics (CX 466, pp. 35359, 35361, 35374, 35377–78); (2) the 1971 and 1973 editions of the *AMA Drug Evaluations*—a journal recognized by respondent as a reliable source of information on drugs (CX 467A and 468B; CX 678, admission 1052); and (3) the *Medical Letter,* a recognized publication relied upon by physicians and other scientists for information relating to the performance of therapeutic agents (CX 460A, B; CX 678, admission 1046).

503. The FDA's regulations concerning the bioavailability and bioequivalence of prescription drugs (*Bioavailability and Bioequivalence-Requirements,* 21 C.F.R. 320), do not support respondent's contention that comparative blood level tests are accepted as sufficient basis for predicting the comparative therapeutic performance of different brands of plain 5-grain aspirin. The purposes of the FDA bioequivalence regulations are (a) to identify pharmaceutically equivalent drugs "that are intended to be used interchangeably for the same therapeutic effect and that are not bioequivalent drug products"; and (b) to establish a "bioequivalence requirement for these drug products" (21 C.F.R. 320.50). Thus, "pharmaceutically equivalent drugs" (*i.e.,* drug products that contain identical amounts of identical active ingredients, *see* 21 C.F.R. 320.1(c)) become a concern under the regulations only if they are not "bioequivalent drug products." [123]

504. For purposes of the FDA bioequivalence regulations, Bayer and other well-formulated plain 5-grain aspirin are not only pharmaceutical equivalents, but also bioequivalent drug products. The regulations define "bioequivalent drug products" as pharmaceutical equivalents (or alternatives) "whose rate and extent of absorption [*i.e.,* bioavailability] do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions. . . ." The regulations further note that:

[s]ome pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the *extent* of their absorption but not in their *rate* of absorption and yet may be considered bioequivalent because such differences in the *rate* of absorption . . . are considered medically insignificant for the particular drug studied. (21 C.F.R. 320.1(e) (emphasis added)).

505. Differences in the *rate* of absorption become "medically significant" under the FDA regulations (and are therefore viewed as "bioequivalence problems") only if they "would result in therapeutic failure or a hazard to the patient" (42 FR at 1626). Only where such "medically significant bioequivalence problems" exist will pharmaceutical equivalents (such as Bayer and other plain 5-grain aspirin) be found "not bioequivalent" for purposes of the FDA regulations. (*See generally, Criteria and evidence to establish a bioequivalence requirement,* 21 C.F.R. 320.52.) The record does not show that because of any difference in the rate of absorption between Bayer and other correctly formulated plain 5-grain aspirin brands, "therapeutic failure or a hazard to the patient" may result.

506. According to the FDA, the bioavailability of a drug and its efficacy are separate and distinct issues:

It is not . . . the intent of a bioavailability study to demonstrate effectiveness. The purpose of a bioavailability study is to determine the rate and extent of absorption. If a drug product is not bioavailable, it cannot be regarded as effective. However, a determination that a drug product is bioavailable is not in itself a determination of effectiveness. The requirement of evidence of bioavailability is intended to supplement, no[t] replace, clinical evidence of effectiveness. 42 FR at 1640. [124]

* * * * * * *

The bioequivalence regulations are not an attempt to equate evidence of bioequivalence with evidence of relative therapeutic effectiveness . . . 42 FR at 1625 (emphasis added).

507. Respondent's witnesses contended that the FDA's willingness to accept nonclinical data such as dissolution data in connection with its bioavailability and bioequivalence regulations shows the FDA's willingness to accept blood level tests or *in vitro* tests where the effectiveness of a class of drugs (*e.g.,* plain 5-grain aspirin) has been demonstrated (Rhodes, Tr. 11152–54; Banker, Tr. 12566, 13045). However, the FDA's preference for evaluation techniques other than well-controlled clinical trials relates only to the determination of bioavailability or bioequivalence, not comparative effectiveness (42 FR at 1639, 1640). Since clinical tests are not designed to and do not measure the rate and extent of drug absorption, the FDA prefers that a more direct "accurate sensitive [and] reproducible" means of measurement be used where the issue relates to bioavailability rather than to the clinical effects of drugs on patients (42 FR at 1640). In requiring bioavailability data in New Drug Applications ("NDAs") *in addition*

to evidence of effectiveness from clinical trials, the FDA explained that such data is "needed to assure that the dosage formulation intended for marketing has the same characteristics as the dosage formulation used in clinical trials to determine safety and effectiveness and that there is batch to batch consistency." (42 FR at 1639). Thus, clinical tests and bioavailability tests perform different, although complementary, functions. Preference for verification of bioavailability, using evaluation measures other than clinical trials, in no way suggests any relaxation of FDA's clear requirements that issues of safety and efficacy of drugs be determined in clinical trials.

508. The purpose of FDA's bioavailability requirements is to ensure that different batches of an approved drug fabricated by an approved manufacturer, or a chemically identical product fabricated by another manufacturer, be bioequivalent to the original product which had been approved on the basis of well-controlled clinical studies (42 FR at 1632). Therefore, the bioavailability requirements are inapplicable to the question in this proceeding of whether one brand of plain 5-grain aspirin is therapeutically superior to other brands.

509. Aspirin is quickly and easily absorbed into the bloodstream (Rhodes, Tr. 11658, 11750, 11756–58, 11778; RX 318, p. 1054). *In vivo* studies which simply show that one brand of plain 5-grain aspirin is absorbed into the bloodstream more **[125]** rapidly than another cannot support conclusions regarding the comparative speed, intensity, or duration of pain relief afforded by the tested brands. *See* F. 469, 502, *supra.*

510. Respondent was aware of the absence of a scientifically demonstrated correlation between aspirin's blood levels and its analgesic effects during the period of 1969–1974 (CX 678, 722, 723, 734). The medical director for Glenbrook Laboratories during the period of 1971 –1971, Dr. John, testified to his knowledge of this characteristics of aspirin (John, Tr. 5567). The medical director for Glenbrook Laboratories from January 1975 through December 1976, Dr. George Goldstein, also testified to his knowledge of these characteristics of aspirin (Goldstein, Tr. 15608–09).

511. As early as 1957, respondent relied specifically on the absence of such a correlation in challenging competitors' advertising allegedly based on blood level comparisons of OTC analgesic products. In a June 7, 1957 complaint to the Federal Trade Commission, Sterling criticized a competitor's alleged reliance on comparative blood level data for therapeutic superiority claims made for its OTC analgesic product and stated: ". . . there is not a shred of scientific evidence to support the assumption that there is a direct relationship between the salicylate blood level and the actual relief of pain." (CX 371Z008–Z010).

512. Correspondence between respondent and its then advertising

agency indicates that respondent maintained the same view 13 years later. In the September 1, 1970 correspondence, James Luther of Sterling, recommended to Joseph Mack, an official of the advertising agency (CX 678, admissions 52–53), that the following statement be included in a complaint to the networks and the National Association of Broadcasters about a competitor's advertising (CX 347Z050).

> As you well know, blood level studies are not scientifically accepted as the basis for claims pertaining to onset, degree or duration of pain relief. Proof derived from clinical trials is required and insisted upon by the FDA and others whose function it is to weigh and evaluate the sufficiency of analgesic claims. (CX 347Z044–Z046).

On September 18, 1970 Mr. Mack forwarded a complaint to a network about the same advertising (CX 347Z050–Z058), incorporating this passage from Mr. Luther's recommendation (CX 347Z055–Z058). On October 12, 1970, Mr. Mack forwarded to two other networks substantially the same complaint which also incorporated the same passage (CX 347Z059–Z066).

513. Subsequent correspondence between an official of respondent and its advertising agency shows that respondent **[126]** continued to rely on this scientific fact. In November 18, 1973 correspondence, a Sterling official stated that ". . . blood level clinicals have never been accepted as the basis for efficacy claims in the past. We know of absolutely nothing in the medical literature which suggests that a change in this position is warranted." (CX 376A and B).

514. In any event, the comparative blood level data in respondent's possession during the time period of 1969–1974 does not show significantly superior blood levels for Bayer.

515. Respondent relied on a study entitled "Absorption of Salicylate from Ingestion of Various Brands of Proprietary Tablets Containing Acetylsalicylic Acid," by Leon A. Greenberg, M.D. of Yale University Laboratory of Applied Physiology, and E.M. Jellinek (1947) (RX 163). The purpose of this test was to determine relative rates of absorption of salicylate following the ingestion of nine proprietary plain aspirin and combination aspirin tablets (RX 163C).

516. In this crossover study, the investigators measured total salicylate levels in blood samples drawn from nine healthy subjects 2, 5, 10, 15, and 20 minutes after ingestion of aspirin products. The record indicates that the test methodology is deficient in several respects: (1) an inadequate number of subjects (Rhodes, Tr. 11478, 11480); (2) the report's incompleteness, *i.e.,* the absence of graphs which are textually discussed (RX 163W and X; Rhodes, Tr. 11743); (3) the failure to measure aspirin levels (Banker, Tr. 13103); (4) the failure to isolate the source of blood level variations solely attributable to the tested

brands (RX 163R); and (5) the absence of reliability afforded by publication in a peer-reviewed journal (Banker, Tr. 12911).

517. Concerning the plain 5-grain aspirin brands, the investigators reached the following conclusions: (1) salicylate absorption occurs very shortly after ingestion; (2) the rate of salicylate absorption occurring within 20 minutes after ingestion varies among people; (3) within 2 minutes after ingestion, salicylate absorption occurred most frequently with Bayer and Walgreen brands and less frequently with St. Joseph brand; (4) 20 minutes after ingestion, salicylate levels were highest for Bayer and Walgreen and lowest for St. Joseph; (5) subjects who moderately or poorly absorbed salicylate also differentiated to a higher degree among brands than those who quickly absorbed; and (6) Bayer and Walgreen were statistically significantly superior and St. Joseph was statistically significantly inferior to the other brands in terms of ease of absorption (RX 163Z007–Z008). **[127]**

518. Even if this blood level test's deficiencies were disregarded, the utility of the test results is limited because of the admitted shortcomings of the statistical evaluation. One author stated:

> Since there are many sources of variation involved in these tests the task is to isolate the several sources of variation and to arrive at the net variation due to differences in brands. I may state right at this juncture that the analysis leads only to an approximate isolation of different sources of variation, particularly since some of the sources cannot be estimated at all in the present experiment. (RX 163R)

The authors also state that no statistically significant difference was shown between Bayer and Walgreen with respect to ease of absorption (RX 163Z008; Rhodes, Tr. 11744–46). Although they found one brand to be statistically significantly inferior to the other brands, they did not state that other brands, *i.e.*, Whelco, Squibb, Puretest, and Certified, were also statistically significantly inferior (RX 163Z008).

519. Respondent also relies on "Absorption Study of Competitive Aspirin Products," by L. Amsel, an employee of respondent (March 17, 1972) (RX 418). The purpose of this study was to evaluate the absorption and bioavailability of competitive aspirin tablets (RX 418A).

520. In this study, the Sterling employee measured the aspirin and salicylate levels in blood samples drawn from six people at 7, 15, 30, 45, 60, 120 and 180 minutes after ingestion of Korvettes, St. Joseph, and Bayer aspirin tablets (RX 418A). Each brand was represented by two samples, one stored at room temperature and one stored for two months at 70° (RX 418A). The record indicates that the test methodology is deficient in several respects: (1) an inadequate number of subjects; (2) no information regarding the investigator's qualifica-

tions; (3) no information on the protocol; and (4) the absence of reliability afforded by publication in a peer-reviewed journal.

521. Amsel reported the following conclusions: (1) Bayer's peak plasma levels occurred at around 30 minutes while Korvettes' and St. Joseph's occurred at around 45 minutes; (2) of the samples stored at 70°, Bayer and St. Joseph yielded statistically significantly greater aspirin plasma levels than Korvettes at 30–120 minutes; (3) of the samples stored at room temperature, no statistically significant difference appeared among the brands; (4) for area under the curve, St. Joseph yielded about 50%, and Korvettes yielded 50%–75%, less than Bayer; (5) of samples stored at 70°, Bayer and St. Joseph yielded significantly greater salicylate plasma levels than [**128**] Korvettes at 45–180 minutes; and (6) for salicylate plasma levels, no apparent differences existed between Bayer and St. Joseph (RX 418A and B).

522. Analytical methods for yielding precise, sensitive blood levels have been available since the mid-1960's (Rhodes, Tr. 11055, 11835; Banker, Tr. 13055). The scientific literature contains reports, dating from the early 1960's of blood level tests which involved brands of plain 5-grain aspirin (Banker, Tr. 13046–56; Rhodes, Tr. 11788–91). The record indicates that four such articles appeared in peer-reviewed journals, *i.e.,* the *Clinical Pharmacology and Therapeutics,* and the *Journal of Pharmaceutical Sciences,* recognized by respondent's witnesses as highly respected (*see, e.g.,* Rhodes, Tr. 11077, 11140, 11180). At least one, "Aspirin Formulation and Absorption Rate II: Influence on Serum Levels of Tablets, Antacids and Solutions," *J. Pharm. Sci.,* Vol. 53, No. 12, December 1964, by Lieberman and Wood, reported a blood level test which involved more than one brand of plain 5-grain aspirin tablets (Banker, Tr. 13049).

523. During 1971–1974, the Medical Director of Glenbrook Laboratories characterized the blood level data in respondent's possession as "inadequate" to executives of Sterling (John, Tr. 5686, 5708).

524. Respondent also offered a report which appeared in "*In Vitro* Evaluation of Physiological Availability of Compressed Tablets," Wood, Vol. 42, No. 3, *Pharm. Acta. Helv.* (March, 1967) pp. 129–51 (RX 250–Wood). The author did not identify the brands whose comparative blood levels he discussed in the article (RX 250–Wood, pp. 133–34). The author identified the brands as Bayer and St. Joseph in an affidavit (RX 251) which incorporated the text of a March 22, 1978 letter to respondent's counsel (G. Goldstein, Tr. 15777–78). According to this affidavit, the author's article reported the results of the blood level study conducted by Stanford Research Institute. The author indicated that at 20, 45, 90, and 120 minutes, Bayer yielded statistical-

ly significantly superior blood levels to those yielded by St. Joseph (RX 250–Wood, p. 134).

525. Even if the comparative blood level data discussed above were considered to show that Bayer produced statistically significantly superior blood levels to those produced by other plain 5-grain aspirin brands tested, this data would not serve as a reliable basis for predicting the superior therapeutic performance of Bayer. Dr. Banker, respondent's expert witness, testified that statistically significant differences should be evaluated for their "operational significance" (Banker, Tr. 12905), meaning clinical significance. Since the clinical significance of aspirin's blood levels to its analgesic action has not been demonstrated, the comparative blood level data **[129]** reviewed here does not constitute a reliable basis for predicting the comparative therapeutic performance of different brands of plain 5-grain aspirin tablets (F. 469, 502, *supra*).

526. During the period of 1969–1974, certain official standards, adopted by the FDA pursuant to the 1962 amendment to the Food, Drug & Cosmetics Act, applied to the manufacturing and marketing of plain 5-grain aspirin tablets in this country. Compliance with these standards was a legal requirement for marketing of aspirin tablets by manufacturers and distributors (*see, e.g.,* Miller, Tr. 7176; Banker, Tr. 12601–02). These standards included requirements established by the United States Pharmacopeia Convention ("USP") and in the FDA's Good Manufacturing Practices regulations ("GMPs") (Banker, Tr. 12573). Both sets of requirements were subject to enforcement by the FDA (*see e.g.,* Miller, Tr. 6944–57; Rhodes, Tr. 11138; Banker, Tr. 12573–75).

527. The purpose of the USP standards for aspirin is to ensure that aspirin products manufactured in this country are of a certain level of pharmaceutical quality with respect to their composition, purity, potency, stability and safety (Miller, Tr. 6678; Banker, Tr. 12530). To this end, the USP has established standards for certain *in vitro* characteristics, such as disintegration, aspirin content, and FSA levels (Miller, Tr. 6733; RX 151C). The USP monograph for aspirin has undergone review and revision from time to time. For example, a dissolution standard for aspirin products was added in 1980 (Banker, Tr. 12735–39; RX 151).

528. The FDA's GMPs, 21 C.F.R. 133 (April 1, 1979), contain requirements of a more comprehensive and general nature concerning the quality of manufacturing practices employed by drug firms. They apply to the maintenance of manufacturing facilities and equipment, qualifications of personnel, quality control procedures, and stability testing. These requirements have also undergone review and revision. For example, an expiration date requirement for 5-grain aspirin was

added in 1976 (Banker, Tr. 12589). Pharmaceutical companies which manufacture or distribute solely OTC drug products, formerly exempt from the GMP regulations, recently became subject to these requirements (*see, e.g.,* Rhodes, Tr. 11618).

529. If a drug manufacturer or the FDA discovers a drug product failing to meet the USP standards or the GMPs, either the manufacturer or the FDA can initiate a recall of the product (Miller, Tr. 6941–42).

530. It is generally recognized that the FDA's compliance monitoring and enforcement programs have been very modest over the years, especially with respect to OTC drug products. However, the FDA regularly publishes bulletins and notices of recalls and seizures of drug products, including aspirin [**130**] products. The bulk of aspirin seizures have been due to failure to comply with the GMPs.

531. The fact that different brands of aspirin are required to meet official standards does not mean that they are in fact either therapeutically equal or unequal (Banker, Tr. 12600, 12848, 12892–93; Rhodes, Tr. 11130, 11189). GMPs do not address the issue of ultimate therapeutic effect (Miller, Tr. 6947; Banker, Tr. 12576). Official product standards or manufacturing standards do not measure drug efficacy (Miller, Tr. 6928; Rhodes, Tr. 11112, 11282, 11295). Such physical and chemical data alone do not guarantee effectiveness (Banker, Tr. 12702). Meeting official standards or achieving supra-official standards, while important and desirable, does not address the question of whether one brand of USP 5-grain aspirin is therapeutically superior to other brands.

532. In recent years, as a result of several highly publicized and serious instances of bioavailability problems involving important drugs and potentially life-threatening conditions (such as digoxin and certain antibiotics) the issue of physiological or biological equivalence (bioequivalence) of pharmaceutically equivalent drug products has come to receive much attention from the medical scientific community in general and the pharmaceutical research community in particular (RX 259–Skelly; RX 250–Hodges; RX 250–Castle; RX 250–Ad Hoc; RX 250–Copper).

533. This concern focusing on the issue of bioequivalence of pharmaceutically equivalent drug products (having identical active chemical formulations) spurred new research in the emerging sciences of biopharmaceutics and pharmacokinetics. Biopharmaceutics is concerned with pharmaceutical factors influencing the disintegration, dissolution, and absorption of active ingredients in drug products. This concern has led to a detailed and critical inquiry into the manufacturing technology and physicochemical elements which bear on drug dissolution and absorption, including materials and equipment,

fabrication and tableting technology, and quality control procedures. Pharmacokinetics is concerned with metabolism of active drug ingredients in the human body, including all the principal phases of absorption, biotransformation, distribution, tissue adhesion, excretion and elimination. This concern has led to a detailed and critical examination, often with the aid of new technology and procedures, of important metabolic characteristics of various drugs. As a result, the 1970's have produced an explosion in the bioavailability literature and brought about a heightened awareness of the bioavailability and bioequivalence issues not only among the academic and research community, regulatory agencies and the drug industry, but also among practicing pharmacists and clinicians (F. 532, *supra;* OTA Report, RX 158 [official notice was taken of RX 158]). **[131]**

534. At the request of the American Pharmaceutical Association made in December 1971 and June 1972, the Joint Ad Hoc Committee on Drug Selection of the Academy of the General Practice of Pharmacy and the Academy of Pharmaceutical Sciences compiled in October 1972, and published in June 1973, "An Annotated List of Drugs With a Potential for Therapeutic Inequivalence Based on Current Evidence of Drug Product Bioavailability Inequivalence." (RX 250–Ad Hoc). The preamble of the List stated in part:

> Present evidence indicates that different products of certain drugs (e.g., different dosage forms or different brands, sources or lots of the same drug dosage form) may have a potential for therapeutic inequivalence due to differences in bioavailability even though these products meet existing judicial and compendial standards. This potential may be a result of inherent properties of the drug or dosage form, the materials and methods used in manufacture and/or the clinical circumstances in which they are used. Those drugs for which bioavailability data are available have been listed in a "high," "moderate," or "low risk" category based on the criteria and clinical implications noted noted . . . This list is intended only as an alerting system and is not suggested to provide all necessary information for these decisions.

535. The Ad Hoc Committee listed "aspirin (when used in high dose levels, *e.g.,* in the treatment of rheumatoid arthritis and rheumatic fever) particularly when given as enteric coated tablets" in the "high risk potential" category. The Committee's criteria for "high risk potential" is set forth as:

> Drugs used in very critical therapeutic situations and which have documented evidence of inequivalency. Inequivalence may lead to serious adverse effects. (p. 280, stamped 29)

The Committee further explained the "implications" of a "high risk potential" listing as:

Selection of product for initial therapy should be based on documented evidence of optimal bioavailability or clinical effectiveness as compared to a reference product with well-established clinical efficacy. This information should be available to and evaluated by a knowledgeable [132] pharmacist. Product interchange during therapy should be done in consultation with the attending physician and then only when sufficient information is available to the pharmacist on the bioavailability of the substituted product and/or an adequate surveillance is possible by reliable measurements of clinical or pharmacologic response. (*Id.*).

536. In February 1977, the American Pharmaceutical Association published its first "Bioavailability Monograph on Aspirin." (RX 250–Mayerson). The APHA monograph notes the bioavailability of aspirin products and its clinical significance and states in part:

Since the salicylate elimination rate is a function of the dose ingested, relatively small increases in dose result in more than a proportional increase in body salicylate levels. For example, a twofold increase in the daily salicylate dose from 2 to 4 g may result in a fourfold increase in body salicylate levels.... This observation is particularly important in patients who require large daily aspirin doses for various chronic conditions, especially as the amount of drug in the body often approaches toxic levels. Under such conditions, minor changes in aspirin bioavailability have a profound influence on the patient's therapeutic status. As a result of this unusual dose-dependent pattern of salicylate accumulation, relatively small changes in dose or bioavailability produce marked and greater than expected changes in therapeutic response as well as increased toxicity.

537. The record also includes references to RX 250–Koch-Weser. J. Koch-Weser, "*N.E. J. of Med.*, 291(10): 503–506 (1974), a brief review article, lists "Aspirin" in "Table 4. Drugs for Which Bioequivalence between Differing Products Has Been Demonstrated," (p. 504) and "Table 5. Drugs for Which Therapeutic Inequivalence between Different Products Has Been Demonstrated" (p. 505). However, Koch-Weser's textual discussion is clear that the author's reference to aspirin is limited to its use as "anti-inflamatory" drug at high dose levels (p. 505).

538. The record discussions of elimination kinetics of aspirin and its clinical implications are limited to chronic use of aspirin at very high and near toxic levels, far exceeding the maximum daily doses of aspirin recommended by the FDA's Panel on [133] OTC Internal Analgesic, Antipyretic and Antirheumatic Products (CX 466 at 35358).

539. In discussing RX 250–Koch-Weser, Dr. Danhof, respondent's witness, agreed that demonstration of statistically significant differences in the bioavailability of one drug product from another does not prove that these products' therapeutic performance would differ in a clinically important fashion (Danhof, Tr. 17270). Thus, bioinequivalence does not necessarily imply therapeutic inequivalence (Danhof Tr. 17270; RX 250–Koch-Weser, p. 504). Another witness for respond

ent, Dr. Rhodes, stated that, if a bioequivalence problems exists for aspirin when taken for analgesia such a problem has not been sufficiently defined or documented (Rhodes, Tr. 11176).

540. The FDA has not promulgated a bioavailability monograph for plain 5-grain aspirin (Rhodes, Tr. 11812; Banker, Tr. 12932–33). Respondent's witnesses, Drs. Rhodes and Banker, disagreed over whether the FDA has informally considered aspirin, when taken for analgesia, as posing a potential bioavailability problem. Dr. Rhodes testified that in recent discussions with representatives of the FDA concerning bioavailability problems, these representatives did not express such a concern about aspirin (Rhodes, Tr. 11813). Dr. Banker testified that the FDA was "very concerned" about aspirin (Banker, Tr. 12555).

541. Thus, this record contains no reports of therapeutic inequivalence among different brands of plain 5-grain aspirin, meeting official standards, when taken for OTC use. In addition, the Medical Director of Glenbrook Laboratories during 1971–1974 was unaware of medical literature suggesting or concluding that therapeutically significant differences might arise among different aspirin brands which met official standards (John, Tr. 5657, 5692).

Dissolution

542. It is important to note here that, as important as the physicochemical characteristics of aspirin tablet may be to dissolution and absorption, the bioavailability of aspirin in the human blood is also determined, to a great, if not greater degree, by the complex and infinite human variability among individuals. Such variables include, among others, age, body weight, stomach content pH, liver function, individual metabolic rate and characteristics, and urinary excretion. It is fair to say that even when the materials, fabrication and tableting technology with respect to aspirin products are perfected, the question of bioequivalence and bioavailability, to *the extent it may exist with respect to aspirin* (*i.e.,* high maintenance doses in the treatment of rheumatoid arthritis and rheumatic fever, especially with enteric-coated aspirin) is likely to remain. Hence, the paramount necessity for determination of optimal doses for each individual through careful titration by [134] physicians, when aspirin products especially the enteric-coated) are being used at high dose levels for he treatment of rheumatoid arthritis and rheumatic fever.

543. It is an accepted principle of biopharmaceutics that the manner in which an aspirin tablet or any other drug is manufactured, including its physical and chemical characteristics, may affect the speed and nature of disintegration as well as the dissolution rate of the drug in tablet form. There appear to be measurable differences in

the rates of disintegration and dissolution among aspirin brands. The more rapid the dissolution of an aspirin tablet, the more likely the rapid absorption into the bloodstream. There appear to be measurable differences in rate of absorption among commercially available 5-grain plain aspirin tablets. It is a known principle that the rate of dissolution of a tablet can be influenced by the manufacturing processes and methods of making a tablet and its physical and chemical characteristics (Danhof, Tr. 16934–36).

544. The significance of comparative dissolution data is best understood by a discussion of the series of events which must take place for a drug to go from the tablet into the patient's bloodstream. A tablet first enters the stomach, and disintegrates, forming a very fine cloud of particles. The drug then must dissolve in order to cross the wall of the gastric mucosa and enter the bloodstream. This is absorption. Because aspirin is a hydrophobic drug, absorption is rapid, and thus, the rate-deciding step in getting the drug from the tablet into the bloodstream (absorption) is dissolution. At first, disintegration tests were the only tests applied to compressed tablets. Subsequently, it became increasingly obvious that there were more important absorption differences between a number of different drug products which contain the same drug substance. Therefore, the dissolution parameter has become of increasing importance in recent years (Rhodes, Tr. 11433; Feinstein, Tr. 16480; Danhof, Tr. 17067).

545. It is a recognized principle that the rate of dissolution of an aspirin tablet is the controlling factor relating to the rate of absorption. Thus, the faster the dissolution of the aspirin tablet, the more likely the rapid absorption of the tablet into the bloodstream (Danhof, Tr. 16989, 16992, 17067, 17011–12, 17067; CX 466 at p. 35470). However, the methodology has not been developed whereby we can determine with precision the exact amount of salicylates in the bloodstream required in a given patient to produce pain relief. Respondent's expert witness testified that it is, therefore, appropriate to look at such factors as the dissolution rates of different brands of aspirin to make a judgment relating to their therapeutic performance (Danhof, Tr. 17101–06).

546. Complaint counsel's and respondent's expert witnesses agreed that it is a basic principle in medical science that in [**135**] order for a drug to provide therapeutic relief, it must be absorbed in such a manner that allows a minimum threshold level to be reached in the bloodstream (Rickels, Tr. 8033–34; Danhof, Tr. 17059, 17060).

547. The principle of a threshold for minimum efective concentration level in the bloodstream is recognized and frequently discussed in the scientific literature (Danhof, Tr. 17060). For example, in the article, Koch-Weser, "Therapeutic Importance of Bioavailability Fac-

tors," *N. Eng. J. Med.*, 291:503 (1974), it is noted that a "minimum effective concentration" of analgesic drugs must be reached in order for the drug to be therapeutically effective (Danhof, Tr. 17060–61; RX 250–Koch-Weser, p. 503).

548. Failure of an aspirin tablet to reach the threshold or minimum effective concentration in the bloodstream would result in that tablet providing no therapeutic relief (Danhof, Tr. 17068, 17087–89). For example, in RX 250–Calabro, "Fever Associated With Juvenile Rheumatoid Arthritis," *N. Eng. J. Med.*, 276(1):11,15 (1967), an aspirin dosage had no effect on a patient's high fever until the dosage was increased 10%–12%, thus clearly demonstrating the minimum threshold principle (Danhof, Tr. 17087).

549. The rate of absorption of a drug can affect whether the minimum effective concentration level may be reached in the bloodstream. When a drug is absorbed too slowly, the threshold level may never be reached (Danhof, Tr. 17060–61). In RX 250–Koch-Weser, "Therapeutic Importance of Bioavailability Factors," *N. Eng. J. Med.*, 291:503 (1974), it was noted:

> The rate of absorption is likely to be therapeutically important with single doses. When absorption of a single usually effective dose becomes very slow, the minimum effective concentration of the drug at its site of action may never be reached. This phenomenon has been clearly demonstrated with hypnotic and analgesic drugs. (Danhof, Tr. 17060–61).

550. In order to reach the minimum therapeutic blood level for a proper therapeutic response, the drug must be absorbed at a sufficient rate both in terms of quantity and time, so that the minimum effective blood level will be reached and maintained (Danhof, Tr. 16973, 16975). These principles are well accepted in the scientific community and are set forth in the scientific literature, such as Poole, "Drug Formulation and Biologic Availability," *Seminars in Drug Treatment*, 1(2):148 (1971) (Danhof, Tr. 16972).

551. Although it is not difficult to determine how much salicylate is in the blood, the methodology has not yet been **[136]** developed to precisely determine the minimum threshold salicylate level in the blood necessary to relieve pain in humans (Danhof, Tr. 17068, 17102).

552. The threshold level also varies from individual to individual and for the same individual depending on certain circumstances. Human variability factors affecting the threshold level include differences in metabolism and excretion of aspirin, weight, liver function, pH of the stomach, and pH of the urine (Danhof, Tr. 17288).

553. Factors which affect the absorption of a drug in the same individual include stomach emptying, the presence or absence of food, the time of day, and other materials swallowed with the medication

(Danhof, Tr. 17068–70). Thus, the identical amount of aspirin taken by the same individual would result in that individual having different amounts of salicylates in the bloodstream depending upon the time of day and stomach condition (Danhof, Tr. 17070).

554. Six hundred fifty mg of aspirin (2 tablets of 325 mg aspirin) is the general dosage thought to reach the effective level in most individuals (Danhof, Tr. 17070–72, 17103; CX 466 at p. 35364). To the extent a particular aspirin brand is not absorbed, or fully bioavailable, there is a possibility that the threshold level may not be reached in that given individual so that the aspirin may not provide effective therapeutic relief (Danhof, Tr. 17071–73).

555. One method of making it more likely that the minimum or threshold salicylate blood level will be reached in a given individual is to be certain that the standard tablet contains the full complement of 325 mg of aspirin rather than less (Danhof, Tr. 17074, 17082–83).

556. Another method of making more likely the fact that the threshold salicylate blood level will be reached in a given individual is through pharmaceutical standards which assure that 325 mg of aspirin in a tablet will be 100% bioavailable.

557. Complaint counsel's witness, Dr. Grossman, agreed with the following statement in the FDA-OTC Internal Analgesic Panel Report, CX 466 at p. 35374:

> One might assume that all products containing unbuffered aspirin are comparable with respect to their bioavailability, *i.e.*, the amount of aspirin absorbed into the blood in a given time period. This, unfortunately, has not been demonstrated to be the case. (Grossman, Tr. 7577–78). **[137]**

558. Aspirin, like other drugs, must reach the site of action to be effective. In order to reach the site of action, a drug must be in the bloodstream. A methodology has not been devised to measure in humans the amount of drug at a given site without removal of tissue. Accordingly, scientists measure the amount of drug in the blood to determine the levels that are present at the affected tissue receptor (Danhof, Tr. 17063).

559. The amount of aspirin in the bloodstream over a given period may be plotted on a curve which integrates the blood level with time. There is a school of thought which holds that the area under the curve ("AUC") approximately indicates the "total absorption" of the drug (Danhof, Tr. 17062; RX 418L and M; RX 250–Wood, "In Vitro Evaluation of Physiological Availability of Compressed Tablets," *Pharm. Acta. Helv.*, Vol. 42, No. 3, pp. 120, 134 (1967)).

560. In addition to determining the area under the curve, another factor in evaluating the absorbability of a drug is the level of peaking of the drug in the bloodstream (Danhof, Tr. 17062). When the area

under the curve is similar for two drugs, and the peaks are similar, one can infer similar therapeutic effect. However, when there is a difference in peaks, but equal areas under the curve, this may indicate unequal therapeutic action (Danhof, Tr. 17062).

561. As a member of the USP Revision Committee, respondent's witness Dr. Banker played an important role in setting the USP dissolution standard for aspirin, including the selection of the appropriate apparatus for aspirin dissolution testing. Dr. Banker was requested by the USP to propose a dissolution specification for aspirin. In order to accomplish this task, Dr. Banker relied heavily on a comparative study of aspirin brands performed by the FDA. The results of this FDA study were presented at an American Pharmaceutical Association meeting in 1979 in Anaheim, California, at a session of the "Medicinal Chemistry and Pharmaceutical Analysis Subsection of the Academy of Pharmaceutical Science." On the basis of this and other data, Dr. Banker recommended that the USP standard for aspirin dissolution should be that 80% of the aspirin must be in solution at 30 minutes, using the rotating basket apparatus method (Banker, Tr. 12735–36). Dr. Banker's recommendation was adopted by the full USP, and is currently in force.

562. Dr. Sidney Riegelman is a Professor in the Department of Pharmacy at the School of Pharmacy, University of California, and has received numerous national and international awards for his contributions to pharmacokinetics. He has stated the general principle that "the rate at which a drug reaches the fluid of distribution controls the onset, the intensity, and possibly the duration of pharmacological effects." He has written further that "Many factors involved in this physical state and methods of combining the active components and [138] excipients during the manufacturing of the dosage form caused marked changes in rate of disintegration and dispersion of the granules into the individual particles of drug substance. These processes cause a change in the rate at which the surface becomes available for dissolution." This is a well-accepted pharmaceutical principle (Banker, Tr. 12831–36, citing Riegelman, S., "Physiological and Pharmacokinetic Complexities in Bioavailability Testing," *Pharmacology* 8:118 (1972)).

563. Dr. William H. Barr is an expert on dissolution (Rhodes, Tr. 11089). In a chapter in Griffenhagen, G., *Handbook of Non-Prescription Drugs,* entitled "Internal Analgesics" (1973), Dr. Barr concludes that "changes in formulation which hasten dissolution will provide higher plasma concentrations and a more rapid onset of effect." Dr. Barr further concludes that "The formulation variant of various aspirin products affect not only the rate of absorption, but can also affect the amount of gastric damage producted by aspirin . . . . Gastric

bleeding can be reduced by administering dosage forms which dissolve rapidly . . . ."

564. *The Dispensatory of the United States* (RX 250–Dispensatory) is a well-recognized reference work. It states:

> The rate of dissolution of aspirin in a tablet, for example, will depend on how the tablet has been formulated and prepared. Thus, two products containing the same ingredients and even having the same disintegration time may differ considerably in the rate of dissolution and action. One may produce large particles that remain undissolved in the stomach a long time, causing local irritation. The other may yield fine particles that dissolve rapidly and are absorbed quickly.

(The Dispensatory of the United States, 26th Ed. (1967) at p. 171; 27th Ed. at p. 163; Danhof, Tr. 16982–83).

565. Aspirin is a drug of nonlinear pharmacokinetics, *i.e.,* as increasing doses of aspirin are administered and as the aspirin is absorbed, the first pass of the drug through the liver results in less and less drug being metabolized. At low doses, or if absorption is slow, the aspirin that is being absorbed passes through the liver and is extensively metabolized. At high doses, however, the enzymes responsible for metabolizing aspirin in the liver become saturated, and the liver can less effectively handle the aspirin to which it is being exposed. Therefore, the aspirin can pass through in greater quantities and much higher aspirin levels may be achieved (Banker, Tr. 12720–25, citing, Swarbrick, J., *Current Concepts in the Pharmaceutical Sciences: Dosage Form Design and Bioavailability,* Lea & Febiger (1973)). **[139]**

566. Dr. Gerhard Levy is Distinguished Professor of Pharmaceutics at the State University of New York at Buffalo. He is recognized as one of the foremost pharmaceutical scientists, and is one of the founders of biopharmaceutics and pharmacokinetics. These disciplines have shown the importance of dosage form design and pharmaceutical processing as they relate to clinical response (Rhodes, Tr. 11052–54).

567. Dr. Levy has stated, in a more conservative vein than Dr. Barr, that, "The onset, intensity, and duration of many pharmacological effects, including analgesia, are related to the magnitude and time course of drug levels in the body (among other factors), and it is likely, therefore, that the analgesic effectiveness of aspirin is a function of the time course of aspirin levels in the body." Dr. Levy further recognized that the absorption rate of aspirin can be affected by physiological and pharmaceutic dosage form factors (Banker, Tr. 12699–700; RX 250–Levy (1965)).

568. Dr. Levy further concluded that, "Clearly, different aspirin tablet preparations, which release the drug *in vivo* at different rates,

will yield maximum drug levels differing both in magnitude and in time of occurrence. The maximum aspirin levels obtained after administration of aspirin in tablets, which result in rapid drug absorption, may be more than twice as high as the levels obtained with tablets having slower drug release characteristics." Dr. Levy concluded that, "Differences in the absorption rate of aspirin will have a marked effect on the magnitude of maximum aspirin blood levels, but only a minor effect on the magnitude of maximum total salicylate levels." Therefore, if high aspirin blood levels are desired, it is important to have a rapid absorption rate (Banker, Tr. 12707; RX 250–Levy (1965)).

569. According to Dr. Banker, the FDA has recommended drug products with rapid absorption profiles, because such products are believed to enhance consistency of absorption and bioavailability. By having rapid dissolution rates, such drug products can reduce the impact of physiological factors that can adversely influence absorption, including rate of transit along the gut, stomach emptying time, presence and absence of enzymes, and variations in pH (Banker, Tr. 12600–01).

570. With respect to a general definition of therapeutic superiority, Dr. Miller stated, "In this case, it will be based on the absorption characteristics of the drug, which, in turn, would lead to a conclusion that if it is absorbed well, it would reach its best therapeutic effect that could be achieved with that drug." (Miller, Tr. 7150).

571. According to Dr. Levy, aspirin in rapidly absorbed form is a more effective analgesic than the same drug given in [**140**] more slowly absorbed form. According to Dr. Levy, the clinical significance of such differences cannot be assessed at this time, since current analgesometric methods are apparently not sufficiently sensitive (RX 250–Levy (1965)). However, it is also possible that such differences, to the extent they may exist, are too small to have any statistical or clinical significance.

572. Dr. Banker agreed with Dr. Levy's position, and said that this position is confirmed by the *Handbook of Non-Prescription Drugs,* the FDA-OTC Internal Analgesic Panel Monograph (CX 466), and the APHA Bioavailability Monograph (RX 250–Mayerson). Dr. Banker testified that the relationship between the pharmaceutical quality of aspirin tablets and their absorption is a documented scientific fact (Banker, Tr. 12697–701, citing, Barr and Penna., "Internal Analgesics," in Griffenhagen, G., *Handbook of Non-Prescription Drugs* (1973)). With respect to aspirin, however, there is no dispute that a direct correlation between salycilate blood levels and the onset, duration or intensity of analgesia in humans has not been demonstrated. Therefore, blood level data is insufficient to support a firm conclusion re-

garding the issue of comparative efficacy among aspirin products. *See* F. 469, 502, *supra.*

573. Aspirin is the drug of choice for treating arthritic and rheumatic conditions such as rheumatoid arthritis and rheumatic fever (*see, e.g.,* CX 466, p. 35462). Although aspirin is available for OTC purchase, the FDA Panel on OTC Internal Analgesics unanimously stated in its 1977 Report, CX 466, that use of aspirin for antirheumatic or anti-inflammatory therapy is medically appropriate and safe only under medical supervision. The FDA Panel also stated that self-diagnosis and self-treatment by consumers with arthritic and rheumatic conditions is medically unsound and potentially dangerous (CX 466, pp. 35453–54). Dr. Banker, respondent's witness, agreed with the Panel's statements and acknowledged the FDA Panel Report as the "most official document on analgesic activity" (Banker, Tr. 12695).

574. The scientific community recognized the use of aspirin for arthritic and rheumatic conditions, as appropriate only in the context of ongoing medical supervision. The major reasons for this view are that diagnosis of rheumatoid arthritis is complex and requires physicians' skill and experience, that each condition is unique and that each patient is physiologically different from another (CX 466, pp. 35453–54). For these reasons, physicians titrate each patient, *i.e.,* they gradually adjust aspirin dosage levels to determine the level which provides effective antiarthritic or antirheumatic relief for each patient without inducing toxic side-effects such as tinnitus (ringing in the ears) (CX 466, pp. 35405, 35464; Banker, Tr. 13080–82). [141]

575. Respondent's witnesses, *e.g.,* Drs. Banker and Danhof, agreed that great physiological variability existed among and within people. Specifically, such variability appears among and within people with regard to the rate of absorption and the rate of elimination of aspirin because of individual differences in several respects, *e.g.,* weight, liver functions, pH of the stomach, pH of the urine, stomach emptying time, presence and absence of enzymes, presence or absence of food or other materials (*see, e.g.,* Banker, Tr. 12868, 13053–54, 13078–80, 13097; and Danhof, Tr. 17068–70, 17288).

576. For arthritic and rheumatic conditions, the relationship between the blood levels produced by aspirin and the anti-inflammatory action afforded by aspirin is understood (*see, e.g.,* CX 466, p. 35362). However, an individual patient's blood levels are determined by multiple physiological factors which vary from time to time. Therefore, an individual patient's therapeutic response to a given tablet or tablets of aspirin will vary. Thus, it is impossible to determine the role, if any, that physicochemical differences among aspirin tablets may play in the therapeutic response of arthritic or rheumatic patients. Specifically, it is impossible to determine the clinical significance, if

any, of the differences discussed in this record—in terms of aspirin content and bioavailability—among brands of plain 5-grain aspirin in the treatment of arthritic and rheumatic conditions. For these reasons, this record does not show that any brand of plain 5-grain aspirin, because of its aspirin content or bioavailability, is therapeutically superior to all other brands for treating arthritic or rheumatic conditions.

577. As noted above, one medical concern in treating arthritic and rheumatic conditions with aspirin is the avoidance of toxic side effects. These side effects occur when a patient's salicylate blood level becomes too high for the patient's metabolism to handle (*see* CX 466, p. 35362; Danhof, Tr. 17076–77). The potential for this "blood-level toxicity" is enhanced by aspirin's unusual elimination kinetics (*see, e.g.,* Danhof, Tr. 17076–77). That is, large, sustained dosages of aspirin —which are taken for arthritic and rheumatic conditions, *e.g.,* 4 grams/day more than 10 consecutive days—can saturate the body's elimination or removal mechanisms (*see generally* CX 466, p. 35362). Such a dosage schedule amounts to twelve 325 mg tablets/day and, as such, sharply differs from the common OTC dosage (CPF 695). Once saturation occurs, a subsequent dose of aspirin will produce disproportionate increases in the blood's salicylate levels (Danhof, Tr. 17076–77). In this way, the blood's salicylate concentration can quickly move from effective levels to toxic levels (*see generally* Banker, Tr. 13080–89).

578. Because of the great human variability affecting the rates of absorption and of elimination of aspirin, blood level [**142**] toxicity can occur with any patient and with any brand of plain 5-grain aspirin. Dr. Banker, respondent's witness, agreed and added that any aspirin brand, including Bayer, could result in blood level toxicity (Banker, Tr. 13221). What is fairly clear from this record is that once an optimal maintenance dosage regimen is determined with a particular brand, it would be prudent to stay with the brand used in titration, and that care must be exercised that any new brand to be used is bioequivalent to the brand used for titration. This record does not show that Bayer is safer than other brands of plain 5-grain aspirin when used for treating arthritic and rheumatic conditions.

579. A potential use for aspirin, which has recently undergone scientific investigation, is inhibition of platelet aggregation (*see, e.g.,* Fields, Tr. 16698–702). This research has focused on aspirin's inhibition of platelet aggregation as a possible agent for reducing the likelihood and incidence of, for example, stroke (Fields, Tr. 16540–43). The Internal Analgesics Panel discussed this action of aspirin as well as its attendant side effect, *i.e.,* bleeding (CX 466, pp. 35384–85). Howev-

er, the Panel did not consider this action of aspirin as a recognized indication for OTC use of aspirin (CX 466, pp. 35422, 35450).

580. Thus, matters relating to aspirin's anti-inflammatory and inhibitory actions discussed above are inappropriate for consideration in this proceeding which concerns the advertising of aspirin to consumers for self-treatment.

581. The relationship between the salicylate blood levels and the fever reduction, or antipyresis, is better understood than that between blood levels and analgesia (Danhof, Tr. 17068, 17087–89, 17103). However, the optimal dosage of aspirin for fever reduction remains unknown (CX 466, p. 35445). Additionally, individual fever reduction or suppression can vary greatly among people because of the considerable physiological variability. Therefore, an individual's therapeutic response to a given tablet or tablets of aspirin is determined by numerous physiological factors which vary. Thus, it is impossible to determine the role, if any, that physicochemical differences among aspirin tablets may play in the therapeutic response of individuals with fever. Specifically, it is impossible to determine the clinical significance, if any, of the differences discussed in this record—in terms of aspirin content and bioavailability—among brands of plain 5-grain aspirin in the reduction of fever. For these reasons, this record does not show that any brand of plain 5-grain aspirin, because of its aspirin content or bioavailability, is therapeutically superior to other brands for fever reduction.

582. Additionally, the detection of fever reduction involves an objective measurement (Danhof, Tr. 17088; CX 466, [143] p. 35453). The record does not show that any brand of OTC plain 5-grain aspirin is therapeutically superior to all other brands for fever reduction, or antipyretic action.

583. As noted hereinabove, aspirin is the drug of choice as an anti-inflammatory agent in the treatment of rheumatoid arthritis and rheumatic fever (CX 466, p. 35462). There are many people who have rheumatoid arthritis and who must take substantial amounts of aspirin for long periods of time. Relatively high blood levels of drug are necessary in order to relieve the symptoms of arthritis, but physicians have to be wary of the danger of toxicity. Therefore, the patient must be titrated. If one titrates a patient using a particular aspirin brand, and then the patient switches to another brand, which is not bioequivalent, the purpose of titration may be defeated. It is believed that a substantial proportion of the aspirin tablets produced in this country are used to treat rheumatoid arthritis patients. However, the bioavailability data of different brands of 5-grain aspirin are not publicly available and not known to practicing physicians and pharmacists. In addition, Sterling was not among the firms submitting its

aspirin bioavailability data to the American Pharmaceutical Association in connection with the latter's publication of Aspirin Bioavailability Monograph in 1977 (Rhodes, Tr. 11171–75; Banker, Tr. 12688–96; Scoville, Tr. 14565; RX 250–Ad Hoc Committee Report; RX 250–Mayerson).

584. Dr. Banker testified that, generally speaking, drug products with low bioavailability are subject to increased variability. The greater the variation in bioavailability, the less reliable the product. Therefore, an aspirin product with lower bioavailability would exhibit greater fluctuation of therapeutic effect than would be seen with a product that is completely absorbed. According to Dr. Banker, the FDA generally accepts the principle that where drug products are incompletely bioavailable or poorly absorbed, there would be much greater variation of response in blood level and therapeutic effect (Banker, Tr. 12686–87, citing, Swarbrick, J., *Current Concepts in the Pharmaceutical Sciences: Dosage Form Design and Bioavailability,* Lea & Febiger (1973)).

585. The United States Pharmacopeia XIX in the Preface at page xiii states in pertinent part as follows:

> There is no disagreement with the fact that safety and efficacy and bioavailability, as well as certain other attributes of a drug product, are clearly dependent upon Good Manufacturing Practice in production, so that new tests have been devised and more rigorous standards have been set up for existing procedures with the general objective of improving quality. (Rhodes, Tr. 11108–09). [144]

586. The inert ingredients in an aspirin tablet can affect its bioavailability. Under certain circumstances the pharmaceutical formulation of an aspirin tablet can profoundly affect the therapeutic efficacy of the tablet. The pharmaceutical dosage form can be related to the incidence of gastrointestinal bleeding, secondary to aspirin administration (Moertel, Tr. 6377–78).

587. Dr. Banker testified that, in addition to the physical and chemical stability of an aspirin tablet, one must also consider the so-called "bioavailability stability." This parameter recognizes the fact that the bioavailability of a drug product may change as it ages, and that this change will almost always be in the direction of decreased bioavailability. As an aspirin tablet breaks down, the porosity of the tablet decreases, and this can cause it to have a retarded disintegration-dissolution profile. Dr. Banker further testified that salicylic acid, one of the aspirin breakdown products, has a slow dissolution rate, and is an undesirable component in an aspirin tablet because of its adverse bioavailability and side effects. It has also been suggested that aspirin anhydride, another breakdown product of aspirin, has an adverse effect on dissolution rate (Banker, Tr. 12596–97, citing Zoglio,

M., "Pharmaceutical Heterogeneous Systems III: Inhibition of Stearate Lubricant Induced Degradation of Aspirin by Use of Certain Organic Acide," *J. Pharm. Sci.,* 57:11, 1877–80 (July-Dec. 1968) and Gucluyildiz, "Determination of Porosity & Pore Size Distribution of Aspirin Tablets with Implications to Drug Stability," presentation, Industrial Pharmaceutical Technology Section, APHA, Academy of Pharm. Sci., Atlanta meeting, Nov. 1975, *J. Pharm. Sci.,* 66(3):407 (1977)).

588. Dissolution must occur before absorption into the bloodstream can occur. In order to determine the rate at which aspirin tablets go into solution, dissolution studies are conducted. They typically measure, at various time intervals, the amount of aspirin which has dissolved in simulated gastric fluids or water (*see e.g.,* RX 160B and E).

589. Dissolution data do not show that different aspirin brands are equivalent or inequivalent (Banker, Tr. 13146). The primary importance of a dissolution standard is its correlation, if any, with absorption (Rhodes, Tr. 11749; Banker, Tr. 13039). This important principle is recognized by the FDA in its Bioequivalence Regulations (Rhodes, Tr. 11816–19) and in the scientific literature (Rhodes, Tr. 11824, 11748–50, 11763–64; 11826; Banker, 13039).

590. For plain 5-grain aspirin, a correlation has been demonstrated between dissolution and absorption (Rhodes, Tr. 11687–88; Banker, Tr. 13034; *see e.g.,* RX 250–Wood, pp. 133, [145] 135). Since no correlation has been shown between aspirin's blood levels and its analgesic effects, however, it cannot be said that different aspirin brands' dissolution characteristics predict these brands' comparative therapeutic performance. This scientific fact was attested to by expert witnesses in this proceeding (F. 469, 502, *supra*). In addition, *in vitro* dissolution tests are artificial (Danhof, Tr. 17190).

591. It is recognized in the scientific community that, in formulating hypotheses about likely therapeutic effect, blood level data is more useful than dissolution data (Banker, Tr. 12916; Danhof, Tr. 17197). In addition, respondent's witness, Dr. Rhodes, stated that once dissolved, "it is the same aspirin" (Rhodes, Tr. 11776). It is also agreed that aspirin is a fast releasing drug (Banker, Tr. 12737).

592. The medical director for Glenbrook Laboratories from 1971–1074 believed that the best measure of absorption was blood level tests (John, Tr. 5637). During 1970–1974, the scientific concern was about bioavailability of drugs, not their pharmaceutical characteristics (John, Tr. 1697–98). Dr. John further stated that he had difficulty in accepting clinical conclusions based on *in vitro* studies (John, Tr. 3636).

593. Respondent was well aware of the lack of a correlation between dissolution data and therapeutic effect for aspirin during the period

of 1969–1974. In a 1968 internal memorandum, a Sterling researcher warned that *in vitro* dissolution data ". . . should not be interpreted as being related to the actual *in vivo* situation." (CX 412A). In a 1972 internal memorandum other Sterling researchers reported *in vitro* dissolution data and stated:

> [T]he use of dissolution testing, while stipulated in certain U.S.P. monographs must be interpreted cautiously. There are numerous instances in the literature where no correlation has been demonstrated between *in vivo* and *in vitro* testing. Also, instances appear where there is such a correlation for some and not others of a similar series of dosage forms (e.g., the same tablets made by different manufacturers). Slight differences in technique, when applied to the same dissolution method can be sufficient to give differing and sometimes non-correlatable data. Hence, dissolution data must be interpreted with extreme caution and should not be used as a sole method of measurement of bioavailability. (CX 420A).

In addition, the medical director for Glenbrook Laboratories from 1971–1974 believed that dissolution data could not be translated into therapeutic benefit (John, Tr. 5566). **[146]**

594. Variations within and among lots of a brand provide information about the product's uniformity or consistency (Miller, Tr. 6986–90; Rhodes, Tr. 11651–52; Banker, Tr. 13102). In other words, the more variation, the less consistency. The consistency with which a brand yields a certain dissolution rate, for example, provides information about the reliability of that brand's dissolution rate (*see, e.g.,* Rhodes, Tr. 11450–63). To determine consistency, statistical tests are conducted for standard deviations (Rhodes, Tr. 11450–63, 11651; Banker, Tr. 12905, 13102). Standard deviations provide a more reliable and accurate measure of variability or consistency, than ranges (Rhodes, Tr. 11699, 11703).

595. In conducting scientific investigations, it is important to rule out or to control variables which might influence the property under examination (Banker, Tr. 12904). Thus, it is important to run controlled tests so that a scientist can have confidence in the test results (Banker, Tr. 12904).

596. In any event, the comparative dissolution data regarding plain 5-grain aspirins in respondent's possession during the time period of 1969–1974 does not show a significantly superior dissolution rate for Bayer in comparison with other brands of plain 5-grain aspirin.

597. Respondent offered in this proceeding a set of three reports (RX 160): (1) "Rate of Solution of Aspirin Tablets," by M.E. Auerbach and R.S. Browning, employees of respondent (February 16, 1960) (pp. A-D); (2) "Rate of Solution of Bayer and St. Joseph Aspirin Tablets," by M.E. Auerbach and R.S. Browning (January 28, 1960) (pp. E-F); and (3) "Dissolution Rate of Aspirin Tablets," by H.E. Jorgensen, an em-

ployee of respondent, December 28, 1962 (pp. G-H). The purpose of each test was to compare dissolution rates of several different aspirin tablets (RX 160, pp. A, E, G, respectively).

598. Using laboratory equipment, the investigators in RX 160 measured the percentage or amount of aspirin dissolved at different intervals, *i.e.,* (1) at 30 seconds, 1, 2, 3, 4, 5, and 10 minutes (RX 160A), (2) at 10 and 20 seconds (RX 160E), (3) at 5, 10, 15, 30, 45 and 60 minutes (RX 160G). The test methodology is deficient in several respects: (1) inadequate information concerning the number of samples for each brand; (2) no information about the investigators' qualifications; (3) the absence of reliability afforded by publication in a peer-reviewed journal; (4) the failure to subject the test data to statistical evaluation; and (5) the lack of standard deviation values, *i.e.,* a reliable measure of variability.

599. The investigators in RX 160 reached the following conclusions: (1) at 5 and 10 minutes, respectively, St. Joseph **[147]** yielded 60% and 70% in solution, while Bayer yielded 85% and 96% in solution (RX 160A); (2) at 10 and 20 seconds, respectively, St. Joseph yielded 8.2–10.0, and 16.2–21.6 mg aspirin in solution, while Bayer yielded 19.3–26.6, and 30.0–34.2 mg aspirin in solution (RX 160E); and (3) at 5 and 60 minutes, respectively, the Squibb sample yielded 71 and 272 mg aspirin in solution, while Bayer's samples yielded 90–93, 300–302 mg aspirin in solution (RX 160G). Even if these tests' inadequacies were disregarded, the significance of these tests remains unknown because of failure to perform statistical evaluation. Not only is information about statistically significant differences, if any, unavailable, but also information about lot-to-lot variability, *i.e.,* product uniformity, is unavailable.

600. Additionally, the authors in RX 160 expressed reservations about the use of their laboratory data. In the first test report, the authors advised that their " . . . data [be] checked and double checked first." (RX 160A). In the second test report, the authors advised:

> [B]ut note: if observers friendly to St. Joseph were to pick one certain interval of time, say at 30 or 35 seconds, to take photographs of the two tablets, it is quite possible that the Bayer tablet would still show a small core, whereas the St. Joseph tablet would be completely disintegrated. For this reason, we advise that the data presented above be used with discretion. (RX 160F).

In the last test report, the authors stated that the Squibb sample manifested a dissolution half-life similar to that for the Bayer samples (RX 160G).

601. Respondent also offered in this proceeding comparative dissolution data contained in RX 418. The purpose of this part of the report was to correlate physical (*in vitro*) testing with the human data dis-

cussed in F. 520, *supra.* The investigators measured dissolution rates for both samples of each tested brand. The test methodology, as presented in this report, is deficient for several reasons: (1) no information about the number of samples; (2) no information on the protocol; (3) the absence of reliability afforded by publication in a peer-reviewed journal; and (4) the failure to subject the results to statistical evaluation. Amsel reported that, unlike the Bayer samples, the St. Joseph and Korvettes samples showed a marked decrease in dissolution rate after storage at an elevated temperature (RX 418B). However, the significance of the test results remains in doubt because of author's failure to [148] perform statistical evaluation. Also, the author explicitly added that while Korvette's decrease in dissolution rate coincided with its decreased absorption and bioavailability, St. Joseph's decrease did not do so.

602. The only other comparative dissolution data which respondent offered in this proceeding and possessed during the period of 1969–1974 is that contained in Levy and Hayes, "Physiochemical Basis of the Buffered Acetylsalicylic Acid Controversy," *New England Journal of Medicine,* Vol. 262, No. 21, pp. 1053–58 (May 26, 1960) (RX 318). Dr. Levy is a highly respected pharmaceutical scientist, well known for his research on aspirin during the 1960's and early 1970's (Rhodes, Tr. 11088; Banker, Tr. 12697). The *New England Journal of Medicine,* is a very respected, peer-reviewed scientific journal (Banker, Tr. 12693–94).

603. The investigators in RX 318 sought to determine whether significant variations occurred in the dissolution rates of six brands of plain 5-grain aspirin, one buffered aspirin product, and one salicylate compound (RX 318, p. 1055). For two lots of each product, they reported the amount in solution at 10 minutes, standard deviations, disintegration rates, and dissolution half-time (one value for the two lots) (RX 318, p. 1056). Although the test as reported appears well-documented, the authors do not identify the tested brands of plain 5-grain aspirin (RX 318, p. 1055–56). In a February 2, 1960 memorandum to officials at Sterling, Dr. Tainter identified Bayer as Tablet C (RX 147). Thus, the other brands remain unknown. Levy and Hayes indicated only that the six aspirin brands were nationally distributed as of the time of their writing (RX 318, 1057). This report contains no information about any attempts by respondent to identify the other five brands (*see, e.g.,* Rhodes, Tr. 11450–63).

604. Levy and Hayes concluded that no significant inter-lot differences existed for any product (RX 318, p. 1055) and added that solution rates varied markedly from product to product (RX 318, pp. 1055 and 1057). However, the utility of the test results is limited by the authors' failure to test for statistical significance (Rhodes, Tr. 11798).

Additionally, the data reveal that among plain 5-grain aspirin tablets, Bayer did not yield the fastest dissolution half-time or show the narrowest variability of dissolution rate (Rhodes, Tr. 11945–46; RX 318, p. 1056). Nor did Bayer yield the highest amount in solution at 10 minutes (Rhodes, Tr. 11797; RX 318, p. 1056).

605. During the period of 1971–74, Glenbrook's Medical Director believed that respondent's dissolution data on Bayer was deficient (John, Tr. 5566).

606. During 1969–1974, the literature contained reports of dissolution tests involving plain 5-grain aspirin, which had [**149**] appeared in publications dating from 1960 (*see, e.g.,* RX 318-Levy and Hayes, and RX 250-Wood, p. 133; Rhodes, Tr. 11766–67, 11784; Banker, Tr. 13042). Some of these publications appeared in peer-reviewed journals recognized by respondent's witnesses as highly reputable (Rhodes, Tr. 11077, 11180; Banker, Tr. 12693–94). Dissolution has been a concern in the pharmaceutical sciences for about 15 years (Miller, Tr. 6737; Rhodes, Tr. 11747, 11765–67, 11784–85; Banker, Tr. 12951, 13038, 13040, 13042). A competitor of respondent conducted dissolution tests as early as 1958. In addition, the medical director for Glenbrook Laboratories informed officials at Sterling about publications which appeared in the early 1960's and discussed dissolution tests involving aspirin (John, Tr. 5630).

607. Respondent offered two reports of comparative dissolution data which it acquired after 1974 (RX 195 for identification; RX 287). However, these reports do not corroborate the proposition that Bayer yields a significantly superior dissolution rate to those of other brands of plain 5-grain aspirin. Respondent offered in this proceeding comparative dissolution data contained in RX 195 for identification. In a 1958 report, as reflected in this record, the investigators failed to subject dissolution data for Bayer and St. Joseph to statistical evaluation (Rhodes, Tr. 11496–501, 11731–32). In other reports, the investigators similarly failed to subject to statistical evaluation dissolution data for Bayer and St. Joseph (Rhodes, Tr. 11736–39) and for Bayer and Norwich (Rhodes, Tr. 11501). In a 1956 report, as reflected in this record, the investigators failed to subject to statistical evaluation dissolution data for Bayer and Squibb (Banker, Tr. 13118-19).

608. RX 287 consists of four surveys performed by the FDA's National Center For Drug Analysis (NCDA), St. Louis, Missouri. The authors of the studies were William E. Juhl and Ross D. Korchhoefer. The first survey was a semi-automated analysis of aspirin in bulk and tablet formulations, and an analysis of the salicylic acid content. The first studies involved 170 samples, 58 formulations, and 34 manufacturers with respect to tablets. The bulk aspirin involved 12 manufacturers and 34 samples. The purpose of the study was to determine the

quality of the aspirin and the adequacy of present compendial standards. Part II presents data on three methods for determining the percentage of salicylic acid—the high-pressure liquid chromatographic method, the semi-automated colorimetric procedure (also used in Part I), and the USP method. There were 50 aspirin samples and 34 bulk samples that were analyzed for each of the three methods. In Part III, three kinds of impurities were determined, aspirin anhydride, acetylsalicylsalicylic acid, and salicylsalicylic acid. In Part IV the percent of dissolution of various aspirin formulations were determined at 10-minute intervals running from 10 minutes to 60 minutes. There were 59 [**150**] tablet formulations representing 38 manufacturers (Horner, Tr. 10750–51, 10759–60; RX 287).

609. RX 415 for identification presents the results of Dr. Horner's statistical analysis of RX 287. RX 416 for identification is a compilation of the codes relating to aspirin brands analyzed in RX 287 (Horner, Tr. 10770–98; RX 287, RX 416).

610. With respect to FDA Survey IV, the comparison of the dissolution rates of different aspirin brands, six samples were employed. Two methods of dissolution testing were used, the wire basket and paddle methods. Dr. Banker testified that the paddle method was less reliable, because it was less discriminating than the wire basket method. This is the reason that the USP chose the wire basket method over the paddle method. Therefore, Dr. Banker relied on the FDA data generated by the wire basket study. Furthermore, the paddle method was impractical because all 5-grain aspirins failed the 30-minute according to the paddle method.

611. At 30 minutes, Bayer Aspirin, under the basket method, dissolved at 100.0%. At 30 minutes, Cord brand dissolved at 27.5%. At 60 minutes, Cord dissolved at 52.18%, while Bayer dissolved at 101.4%. Based upon this dissolution data, it is possible to make a judgment that Bayer Aspirin, compared to Cord, is therapeutically preferable (Danhof, Tr. 17098). (The percentages cited above are the percent of the USP standard for aspirin, 325 mg, then dissolved. Because some tablets exceed the USP standard, they register as being more than 100% dissolved.)

612. In the dissolution test results using the wire basket method in RX 287, of 22 brands tested, only Bayer, Squibb and Bowman achieved 100% dissolution. Results for other brands ranged from 14.4% for Pill Mill to 27.5% for Cord to 59.5% for Manhattan, and 93.1% for St. Joseph (Plough). Dr. Danhof testified that because the rate of dissolution is the controlling factor relating to bioavailability of aspirin, data such as RX 287 provides a reasonable basis for a judgment of comparative therapeutic performance (Danhof, Tr. 17097).

613. The record shows that the primary purpose of the FDA-NCDA

aspirin surveys included in RX 287 was to survey aspirin quality and to see whether the various USP standards with respect to aspirin were adequate or some modification or revision was indicated. It was designed as a selective survey and was not intended as a comparative study of aspirin brands. For this reason, the sample selection was predictably haphazard. The dissolution study using the basket method surveyed 59-tablet formulations including 39 brands. The number of samples was inadequate (Miller, Tr. 6986-90; Rhodes, Tr. 11478). It also appears that the investigators used only one lot for each brand, and thus, no information is available on [151] each brand's lot-to-lot consistency (Miller, Tr. 6986–90). The investigators reported that 26.5% of the plain aspirin tablets failed the proposed dissolution test, *i.e.,* 80% dissolved in 30 minutes (RX 287Z057).

614. Even if the sampling inadequacies were disregarded, RX 287 does not show that Bayer showed a significantly superior dissolution rate—by either method—to those of other plain 5-grain aspirin tablets tested. When subjected to statistical analysis by respondent's witness, Dr. Horner (RX 415 for identification), this study revealed that at each time interval, *i.e.,* 10, 20, 30, 40, 50, and 60 minutes, Bayer Aspirin was not statistically significantly superior to all the other plain 5-grain brands tested (Horner, Tr. 10884). At 10 minutes, 6 brands (Bell, Bowman, Freeda, Richlyn, Squibb, and Westward) yielded comparable or better dissolution rates and with more consistency than Bayer (Banker, Tr. 13126). Bell's rate was statistically significantly faster than Bayer's (Banker, Tr. 13126). Squibb's rate was statistically significantly faster than Bayer's (Banker, Tr. 13126). At 30 minutes, two brands (Bowman and Squibb) yielded comparable dissolution rates with more uniformity than Bayer (Banker, Tr. 13127–30). At 40 minutes, Bowman showed 100% dissolution with more uniformity than Bayer (RX 287Z062 and Z068). Dr. Banker explained that values in excess of 100% reflected only analytical error (Banker, Tr. 13128–30). Therefore, Bowman and Bayer had dissolved comparably by 40 minutes. At 50 minutes, Freeda showed a comparable dissolution rate with more uniformity than Bayer (RX 287Z064–Z068). At 60 minutes, Freeda again showed a comparable dissolution rate with more uniformity than Bayer (RX 286Z067–Z068).

615. Dr. Horner failed to test the dissolution data generated by the paddle method in RX 287 for statistical significance (Horner, Tr. 10866–68, 10880). No brand of plain 5-grain aspirin (Bell, Bowman, Ferndale, Stanback, Squibb, and Walgreen) showed higher rates than Bayer (RX 287Z062–69). In addition, the investigators reported that the paddle method had been found historically more discriminating a test for differentiating drug products than the basket method (RX

287Z054). They added that the difference in results for the two methods will be studied in conjunction with an *in vivo* study (287Z057).

616. In any event, the comparative dissolution data discussed in the preceding paragraphs would merely suggest a judgment, but could not support a conclusion that Bayer Aspirin is therapeutically superior to other aspirin. In discussing the comparative dissolution data in RX 287, Dr. Danhof, respondent's witness, stated that one could not judge clinical efficacy based on differences of .2% or .3% in amount dissolved (Danhof, 17196). Also, since no precise correlation has been shown **[152]** between blood levels and the onset, intensity or duration of analgesia, the comparative dissolution data included in the record does not constitute a reliable basis for predicting the comparative therapeutic performance of different brands of plain 5-grain aspirin. *See* F. 469, 502, *supra.*

617. Respondent's witnesses have stated that a fast dissolution rate is also important because this minimizes the possibility of aspirin particles lodging in the gastric mucosa (*e.g.,* Rhodes, Tr. 11649). Further, it has been argued that this effect is important in minimizing the possibility of aspirin-induced gastric damage. Even if these propositions were accepted, the record fails to show that Bayer has a significantly superior dissolution rate to those of other brands of plain 5-grain aspirin. Therefore, the record as a whole does not show that because of its dissolution rate Bayer results in significantly less gastric damage than all other brands of plain 5-grain aspirin.

Tablet Disintegration

618. Disintegration of aspirin tablets must occur before dissolution can occur (Rhodes, Tr. 11689; Banker, Tr. 13009, 13033). To determine the rate at which aspirin tablets break apart, disintegration studies are conducted. Such tests typically measure the time at which a tablet begins and completes disintegration in simulated gastric fluids or water.

619. As with dissolution, the purpose of disintegration is to facilitate the tablet's reaching the bloodstream (Rhodes, Tr. 11751). However, a tablet can disintegrate and yet fail to dissolve (Miller, Tr. 6737; Banker, Tr. 13017). No correlation between dissolution and disintegration has been demonstrated for aspirin (Rhodes, Tr. 11650, 11759; Banker, Tr. 13022; RX 218, p. 1056; RX 250-Wood, p. 151; Moertel, Tr. 6306; Grossman, Tr. 7504; DeKornfeld, Tr. 8417; Danhof, Tr. 17185). The scientific literature contains reports that rapid disintegration does not necessarily lead to rapid dissolution (RX 318, p. 1056; RX 250-Wood, p. 151; John, Tr. 5563; Banker, Tr. 13029). Dr. Danhof, respondent's witness, stated that he would not make a judgment about an aspirin brand's clinical effect based on disintegration time

(Danhof, Tr. 17185). He added that, to be clinically effective, an aspirin tablet need not have the most rapid disintegration rate (Danhof, Tr. 17196).

620. Since the early 1960's, the scientific consensus has been that dissolution, not disintegration, is the rate-limiting factor for aspirin tablet absorption (RX 318, pp. 1054, 1056; RX 250-Wood, pp. 133, 135; Rhodes, Tr. 11450, 11516, 11756–58, 11772, 11786–88). Only abnormally long tablet disintegration times can affect seriously the rate of solution and absorption or the extent of absorption and availability (Miller, Tr. 6737; RX 318, p. 1056). Thus, tablet disintegration data fails to [153] predict dissolution rates, and, hence, their blood levels. Comparative tablet disintegration data similarly fails to predict the comparative therapeutic performance of different brands.

621. During the period of 1969–1974, the scientific literature contained no reports of plain 5-grain aspirin brands which completely disintegrated within five minutes and yet produced different therapeutic effects (John, Tr. 5561; Trout, Tr. 16166–67). No unpublished clinical evidence of such a relationship was available (Banker, Tr. 13025).

622. Furthermore, the comparative disintegration data in respondent's possession during the period of 1969–1974 does not show a significantly superior disintegration rate for Bayer in comparison with other brands of plain 5-grain aspirin.

623. Respondent relied on seven reports of comparative disintegration data, including "Absorption and Disintegration of Various Aspirins," by W.D. Paul, M.D., University of Iowa (1948) (RX 164). The purpose of RX 164 was to determine whether Bayer disintegrated rapidly, and, if so, whether the rapidity was advantageous (RX 164B). In the *in vitro* part of the test, the investigators measured the times at which disintegration began and finished for 19 brands of aspirin, 25 samples each, and Bayer, 100 samples (RX 164J). In the *in vivo* part of the test, the investigators used gastroscopes to observe the disintegration characteristics of Bayer in the stomachs of 63 patients, and 7 other brands, each in 10 patients (RX 164M and N).

624. In the *in vivo* part of RX 164 the investigators reached the following conclusions: (1) Bayer began disintegration fastest (within .985 seconds, on the average); (2) while Bayer tablets uniformly disintegrated into minute particles, many others disintegrated into large, irregular particles; (3) because of the particles' uniformity and minuteness, Bayer tablets presented a larger surface area and would be absorbed quickly from the stomach; (4) of the 63 patients given two Bayer tablets with water, 44 showed ready disintegration; (5) of the seven brands tested in 70 patients for disintegration, two were very poor, three were fair in breaking into large particles, one occasionally

broke up into small or large particles, and one could not be differentiated from Bayer; (6) of all 133 patients, not one showed stomach bleeding following ingestion (RX 1640).

625. The significance of the test results in RX 164 remains in doubt because of the failure to test for statistical significance. It is impossible to determine, for instance, whether Bayer's rate of nearly one second was significantly faster than four other brands' rate of no more than two seconds (RX 164Z015). This failure is also unhelpful in evaluating [154] Bayer's average *in vitro* test performance, derived from 100 samples, with other tablets' averages, each derived from 25 samples (RX 164J; Winig, Tr. 14231–34). The investigator also failed to subject the various brands' rates for complete disintegration to statistical analysis (RX 164Z016). Therefore, it is impossible to determine whether the nine brands (Carter's, McKesson, Squibb, St. Joseph, Parke-Davis, Puretest, Upjohn, Jamieson, and Hobart) which showed faster complete disintegration rates than Bayer were significantly faster than Bayer (RX 164Z015). At any rate, the test data do not show that Bayer has disintegration characteristics superior to those for the other 19 aspirin brands. Nine other brands completed disintegration faster than Bayer. All but two brands disintegrated uniformly much like Bayer (Danhof, Tr. 17182). Also, the investigator noted that, in terms of disintegration characteristics, Squibb could not be differentiated from Bayer (RX 164N).

626. Respondent also offered "Analgesic Tablet Disintegration Report," by Ralph Peimer, M.D. (August 18, 1955) (RX 165). The purpose of this two-part *in vivo* study was to measure the disintegration rates of four analgesic agents. Since this study compared Bayer only with combination products, it affords no information about the comparative disintegration performance of different brands of plain 5-grain aspirin.

627. Respondent also offered "Stability Testing—Commercial Glass Units," by E.J. Mannix, a Sterling employee (April 27, 1970) (RX 159Z024–Z025). The purpose of the test was to determine the initial signs of chemical and/or physical breakdown of Bayer tablets stored under different conditions (RX 159Z024). Since this report contains disintegration data only for Bayer, it affords no information about the comparative disintegration performance of different brands of plain 5-grain aspirin.

628. Respondent also offered "Bayer Aspirin—Stability," by K.R. Klippel, a Sterling employee (November 4, 1971) (RX 176). The purpose of the test was to determine the stability of Bayer, through measurements on 5-year old control specimens (RX 176A and B). Since this report contains disintegration data only for Bayer, it af-

fords no information about the comparative disintegration performance of different brands of plain 5-grain aspirin.

629. Respondent also offered "A. O. Aspirin for Assay, Kress Aspirin Tablets," by E.J. Mannix, a Sterling employee (December 15, 1973) (RX 182). In this test, the investigator studied several pharmaceutical features, including disintegration, of Kress Aspirin tablets (RX 182B). Since this report does not include disintegration data for Bayer, it affords no information about the comparative disintegration performance of different brands of plain 5-grain aspirin. **[155]**

630. Respondent also offered comparative tablet disintegration data contained in RX 318, by Levy and Hayes. As discussed hereinabove, the significance of the test results is limited by the authors' failure to test for statistical significance, and the anonymity of five of the tested aspirin brands. However, the data show that Bayer disintegrated at the same rate as at least four of these brands, *i.e.,* less than 10 seconds (RX 318, p. 1056). The fifth unidentified brand, Tablet D, yielded disintegration rates one to three seconds longer (RX 318, p. 1056). Dr. Banker, respondent's witness, stated that little difference exists between disintegration rates of 10, 11, and 13 seconds (Banker, Tr. 13021).

631. Respondent also offered comparative tablet disintegration data in RX 418. Prior to conducting the blood level test, the investigators measured samples of each brand for rate of complete disintegration. They reported disintegration rates of less than .5 minute and 2–7 minutes for Bayer, less than .5 minute and more than 30 minutes for St. Joseph, and 4-5 minutes and more than 30 minutes for Korvettes (RX 418J). Since the investigators failed to subject this data to statistical analysis, however, it is impossible to determine whether this resulted from chance or differences directly attributable to the brands.

632. Respondent also offered "Commercial Aspirin Tablets," by C. A. Kelly, a Sterling employee (June 1, 1972) (RX 177). The author did not state the purpose of the test(s) reported here. An investigator measured Bayer and five other aspirin brands for various pharmaceutical characteristics, including tablet disintegration (RX 177). The investigator reported Bayer, represented by two lots, and three brands, *i.e.,* Medico, Kor-Val, and Saxon, represented by one lot each, completely disintegrated in less than .5 minute. Two other brands, *i.e.,* Nosco Hygrade, and York, yielded rates of 15–32 minutes and 1–60 minutes (with one tablet failing to disintegrate), respectively. The significance of the test results remains in doubt because of the failure to perform statistical evaluation. This report is additionally limiting because only Bayer was represented by more than lot (Banker, Tr. 12979).

633. Other reports of tests comparing Bayer with other aspirin

brands for tablet disintegration rates which were in respondent's possession from 1969–1974 included CX 448, the "223 Study." As discussed hereinafter, the results of the "223 Study" do not provide a basis for a firm conclusion due to serious methodological problems. At any rate, the tablet disintegration data in RX 448 does not show that Bayer is significantly superior to the other 220 aspirin brands. McKesson, Norwich, Rexall, St. Joseph, and Upjohn began disintegration within 2 seconds and completed disintegration [**156**] within 30 seconds (CX 448Z004). The author reported rates for all six brands as "pass" (CX 448Z004). Dr. Danhof, respondent's witness, stated that on the basis of this test he would not make a judgment that Bayer is therapeutically superior to the other aspirin brands (Danhof, Tr. 17179). In addition, 39 of 40 Squibb samples achieved the same rate. Statistical analysis indicated that Squibb was not statistically significantly different from Bayer (CX 448Z004). Also, the investigators reported that 16 minor brands accomplished disintegration at the same rate as Bayer (CX 430B; *see* CX 448Z027).

634. Respondent also had in its possession "The Quality of Aspirin Tablets," by J. Winig and G. Prince, Sterling employees (early 1960's) (Winig, Tr. 14224–30) (CX 445). The purpose of the study was to explore variations in commercial brands of 5-grain aspirin tablets along several parameters of pharmaceutical quality and elegance, including disintegration (CX 445C and Q). With respect to disintegration, the investigators reported that the major brands (Bayer, Squibb, McKesson, St. Joseph, Rexall, and Norwich (CX 445A)) showed very good speed of disintegration (CX 445S). All samples for two brands (McKesson and Rexall) completed disintegration by 30 seconds whereas one Bayer sample and one Norwich sample did not (CX 445T). They added that 111 of 146 minor or regional brands completed disintegration within 30 seconds. Thus, the data show that Bayer did not disintegrate faster than the other 152 aspirin brands (CX 445T).

635. Respondent also relied on RX 138, entitled "Analysis and Evaluation of Bayer Aspirin with Various Other Brands of 5 Grain Aspirin as Found in the United States Homes," by Dr. Herbert Terry of Foster D. Snell, Inc. in 1972 (the "Snell Study"). Foster D. Snell, Inc, is a consulting organization which specializes in the provision of a broad variety of services to the chemical, manufacturing, pharmaceutical and food industries. Snell was a division of Booz, Allen & Hamilton, a major international consulting firm. As of 1978, Snell had been in existence approximately fifty years, and had served well over 9,000 clients. The primary focus of Snell's activities was the conception and evaluation of new chemical research and development, biology, bacteriology, pharmacology and toxicology; evaluation of foods, cosmetics, tioletries, chemical engineering and production

expertise; and economic marketing and general business analysis. It is a reputable, independent testing firm with a high standard for reliability and is well recognized in the pharmaceutical field (Terry, Tr. 10919–20, 10932; Rhodes, Tr. 11443; Banker, Tr. 12784; RX 413. complaint counsel's admission nos. 509, 316).

636. The Biological Sciences Division of Snell specialized in providing services dealing with biological evaluations. It had a fully equipped animal laboratory, microbiological support capabilities, and a staff equipped to evaluate and carry out biological testing and development. At the time of the [157] performance of the Snell Studies, Dr. Leonard Sheffner was the head of the Biological Services Division. He had a Ph.D. degree from the University of Illinois Medical School, and had served as the principal investigator for the American Cancer Society. He had a wide background in pharmacological and biological studies (Terry, Tr. 10920–21; Foster D. Snell, Inc., "Product and Process Development").

637. Approximately a dozen Snell personnel worked on the studies. They were familiar with pharmaceutical testing procedures (Terry, Tr. 10937).

638. Dr. Sheffner and the Biological Sciences Division of Snell were involved in establishing the soundness of the design and determining that the parameters measured were significant to the quality of the aspirin products. In addition, there was a statistical consultant, Dr. John Dutt, who had worked closely with the Biological Sciences people on other studies, who reviewed the statistical design and approach (Terry, Tr. 10933).

639. Crossley Surveys is an organization which carries out market research studies, largely for consumer product firms. They have a good reputation for carrying out competent and reliable studies in this area. They designed the statistical sample and collected the actual aspirin samples from the American homes in RX 183–184 (Terry, Tr. 10931–32). It was determined by all parties that the most useful method of analyzing aspirin brands would be one which reflected the condition of the various brands as they were actually found in the home at the time of use (Terry, Tr. 10932–34).

640. The sampling technique used by Crossley sampled the universe of private households using an advance multi-stage, stratified area probability technique. This method produced valid and reliable data representative of households in the United States and samples of aspirin products in such households (RX 339–Leonard; Terry, Tr. 10933).

641. The code for the Snell Study (RX 183) was as follows: A is Norwich; B is St. Joseph; C is Squibb; D is Rexall; E is McKesson. The study compared Bayer Aspirin with competitive aspirin brands, and

found that Bayer had significantly fewer erosion and breakage effects, less acetic odor, a whiter tablet, higher aspirin content, a lower percentage of free salicylic acid, a faster starting time for disintegration, and a faster time for complete disintegration (Terry, Tr. 10937).

642. Using the Bayer Aspirin product specifications, Bayer also had fewer failures than other brands in terms of tablet color, aspirin content, free salicylic acid and disintegration. All Bayer Aspirin passed every USP requirement, while a total or 4.9% of the samples of the other brands failed one or more USP tests. There was greater product uniformity among containers [158] of Bayer than among containers of other aspirin brands (Terry, Tr. 10952–54, 10937, 10961; RX 183).

643. Based on his experience in comparative evaluation of consumer products, Dr. Terry testified that it is rare in evaluating a group of products which are competitive in the marketplace to find the type of superiority for a single brand which was demonstrated for Bayer Aspirin in the Snell Studies (Terry, Tr. 10960). Dr. Terry further testified that the methodology of the studies was valid at the time it was done, and that he would employ essentially the same method if he were asked to retest the products today (Terry, Tr. 10960; RX 183). Drs. Rhodes and Banker testified that the Snell Study substantiated the results of the 223 Aspirin Study (RX 448).

644. However, the Snell Study has several problems: (1) failure to blind; (2) no information about most of the personnel involved in testing; and (3) the application of an unusual mathematical evaluation technique, which is based on certain assumptions not shown to be valid in this record.

645. More specifically, the investigators in the Snell Study reached the following conclusions concerning one tablet disintegration test (RX 183Z021): (1) Norwich and McKesson began disintegrating as fast as Bayer; (2) St. Joseph, Squibb, and Rexall began disintegrating in a slightly longer time period; (3) Norwich, St. Joseph, and McKesson completed disintegration at rates significantly lower than that for Bayer; (4) Rexall completed disintegration at a rate similar to Bayer's while Squibb did so at an appreciably slower rate than the others; (5) Norwich produced no failures in this test, while Bayer and the other brands did (RX 138Z020). Concerning a second tablet disintegration test (RX 183Z022), the investigators reported: (1) Norwich, St. Joseph, and Rexall yielded the fastest times for complete disintegration; (2) Bayer and McKesson yielded slightly lower rates, while Squibb was considerably slower; and (3) Norwich, St. Joseph, McKesson, and Bayer exhibited no failures on this test while Squibb and Rexall did (RX 183Z022). These data, however, do not show that Bayer is statisti-

cally significantly superior in disintegration rate to all 221 tested aspirin brands (RX 183G).

646. The first disintegration test (RX 183Z021) showed: (1) Norwich, McKesson, and St. Joseph began disintegration at rates not statistically significantly different from Bayer's; (2) Squibb and Rexall began disintegrating within less than one second after Bayer; (3) Rexall completed disintegration at a rate statistically insignificantly different from Bayer's; (4) Norwich began disintegration with more uniformity than Bayer; and (5) Norwich and St. Joseph completed disintegration with more uniformity than Bayer (RX 183Z021). The author's application of game theory showed that Norwich, St. Joseph, McKesson and Bayer received the highest possible "utility **[159]** rating" for beginning disintegration (RX 183Z021). The author also noted that Norwich, St. Joseph, Rexall, and McKesson received higher "utility ratings" than Bayer for completing disintegration (RX 183Z021).

647. The second tablet disintegration test (RX 183Z022) showed that four brands (Norwich, St. Joseph, Rexall, and McKesson) complete disintegration at rates faster than Bayer's. Since the author failed to subject this set of data to statistical evaluation, it is impossible to determine whether the reported differences are merely due to chance. The author also did not apply "utility ratings" to this data (RX 183Z022).

648. Respondent offered two reports of tablet disintegration data which it acquired after 1974 (RX 207 for identification, and RX 215). However, these reports do not support the proposition that Bayer yields a significantly faster disintegration rate than those for all other brands of plain 5-grain aspirin. Respondent offered in this proceeding RX 207 (for identification), a compilation of tablet disintegration data conducted by a competitor, on Bayer and three combination products (Rhodes, Tr. 11473). Therefore, this report affords no information about comparative disintegration performance of different brands of plain 5-grain aspirin.

649. Respondent also offered a set of competitor's in-house reports concerning disintegration problems reported by some of its customers (RX 215). While this set contains disintegration data, it did not deal with different commercially available brands of plain 5-grain aspirin. Therefore, this set of reports offers no information about the comparative disintegration performance of plain 5-grain aspirin.

650. The comparative tablet disintegration data which respondent possessed presents mixed results and thus an inconclusive picture about Bayer's disintegration rate in comparison with those for 220 identified brands of plain 5-grain aspirin. This record does not show

that Bayer yields a significantly superior disintegration rate to those for its major competitors.

651. In any event, comparative tablet disintegration data does not demonstrate superior therapeutic performance of aspirin tablets. Since respondent agrees that dissolution rather than disintegration is the rate-limiting factor with respect to aspirin absorption, the comparative disintegration data is less useful than dissolution data discussed hereinabove and does not constitute a reliable basis for predicting the comparative therapeutic performance of brands of plain 5-grain aspirin. It is also important to point out here again that it is agreed that direct correlation between aspirin absorption and either the onset, intensity or duration of analgesia is yet to be demonstrated. **[160]**

652. One theory advanced in this proceeding is that, in addition to the rate, the nature of disintegration is important (Rhodes, Tr. 11722). Respondent's witnesses, *e.g.,* Dr. Rhodes, stated that Bayer's unique ability to disintegrate into a dispersion of fine particles minimized the likelihood of side effects (Rhodes, Tr. 11571–75, 11651). In theory such a dispersion would enhance a tablet's dissolution rate and minimize the possibility of aspirin particles lodging on the gastric mucosa (Rhodes, Tr. 11378–83, 11772; Banker, Tr. 13199).

653. However, no precise correlation has been demonstrated between disintegration and dissolution for plain 5-grain aspirin. In addition, even if Bayer showed a unique dispersion, it has not been shown that Bayer's dissolution rate is significantly superior to all other brands of plain 5-grain aspirin.

654. In support of the theory discussed above, Dr. Danhof, respondent's witness, relied on his personal experience and published reports concerning the effect of aspirin particle size on the gastric mucosa (Danhof, Tr. 17225–45). However, he conceded that these were not controlled studies, and as such, were open to subjective interpretation (Danhof, Tr. 14241). Dr. Danhof also relied on "Drug Formulation and Biologic Availability," John W. Poole, *Seminars in Drug Treatment,* Vol. 1, No. 2, p. 178 (Sept. 1971) (Danhof, Tr. 17227). Dr. Danhof agreed that Dr. Poole suggested theoretically a number of variables which might influence gastric damage (Danhof, Tr. 17227). He also relied on "Effect of Particle Size on ASA-Induced Gastrointestinal Bleeding," A.Z. Gyory, *The Lancet,* p. 300 (Aug. 10, 1968) (Danhof, Tr. 17225). Yet, on cross-examination, Dr. Danhof faulted this study for involving experimental aspirin formulations rather than commercial aspirin tablets and involving only nine patients (Danhof, Tr. 17237, 17240).

655. Dr. Danhof also relied on his investigations involving dogs (RX 167). In these studies he concluded that crystal size was an important

factor in gastric damage (RX 167Q, U). The utility of animal studies to show comparative safety of pharmaceutical equivalents such as 5-grain aspirin is dubious.

656. Dr. Danhof also relied on an unpublished gastroscopic examination which he conducted in 1979 (Danhof, Tr. 17244–45), in which he compared three aspirin tablets of differing particle size, each administered to 15 patients (Danhof, Tr. 17244–45). He found the aspirin tablet with the small particles to be associated with less blood loss to a statistically significant degree (Danhof, Tr. 17244–45).

657. Scientific evidence exists which indicates that fine particles do not produce less gastric damage than large or [**161**] coarse particles. This evidence appeared in "The Role of Dosage Form in ASA Induced Gastrointestinal Bleeding," Levy and Leonards, *Clin. Pharm & Therapeutics,* Vol. 8, No. 3, p. 400 (1966) (CX 764 for identification; Danhof, Tr. 17227). These investigators are highly respected (Danhof, Tr. 17243; F. 647, *supra*). The journal is a respected, peer-reviewed scientific source (Rhodes, Tr. 11077, 11140, 11180). In this study, the investigators' purpose was to determine the net effect of aspirin particle size on aspirin-induced bleeding in humans (Danhof, Tr. 17228). They compared one finely milled formulation (of 80-mesh and finer) with another relatively coarser formulation (with particles larger than 20 mesh) (Danhof, Tr. 17228). This was a well-controlled study (Danhof, Tr. 17228–34, 17237), which involved double-blinding (Danhof, Tr. 17228). The investigators concluded that, just short of statistical significance, the finer aspirin formulation produced greater blood loss than the coarser aspirin formulation (Danhof, Tr. 17228–34).

658. Dr. Danhof noted that aspirin-induced bleeding, which results from aspirin particles in contact with the gastric mucosa, is a function both of the area and duration of contact (Danhof, Tr. 17228–34). He agreed with the investigators that these two factors appear to cancel one another (Danhof, Tr. 17228–34). He also agreed with the investigators that, where this cancellation occurs, other factors influence the likelihood of gastric damage (Danhof, Tr. 17228–34). He admitted that the duration of contact was, in part, a function of the gastric emptying rate (Danhof, Tr. 17235).

659. Dr. Danhof stated that unless statistical significance at $P < .05$ is shown, he was unable to conclude from this research that particle size was significant (Danhof, Tr. 17241–42). Applying Dr. Danhof's stated rule, this study shows, as the authors concluded, that no statistically significant difference existed between the aspirin-induced bleeding resulting from the fine formulation and that resulting from the coarse formulation (Danhof, Tr. 17241–42).

660. The scientific literature contains no reports showing that dispersion characteristics of different brands of plain 5-grain aspirin

correlate with the degree or incidence of damage to the gastric mucosa (Danhof, Tr. 17186). Dr. Danhof stated that he knew of no statistically significant differences among aspirin particle sizes which related solely to possible gastric injury (Danhof, Tr. 17186). He further stated that not only was more research needed on this question, but also that no consensus exists in the scientific community concerning a correlation of aspirin particle size and gastric distress (Danhof, Tr. 17244–45).

661. No reliable scientific evidence exists which shows that finer aspirin particles produce statistically significantly **[162]** smaller bleeding than coarser aspirin particles. In addition, respondent possessed a report (RX 164) during 1969–1974 which concluded that most of the tested brands of commercially available plain 5-grain aspirin tablets disintegrated in a fashion much like Bayer's, and one brand, Squibb, in a manner indistinguishable from Bayer. Moreover, this report concluded that none of the test brands caused gastric bleeding.

662. Therefore, the record does not show that Bayer disintegrated in a fashion unlike all other brands of plain 5-grain aspirin tested. It also does not show that varying aspirin particle size of different brands has resulted in varying incidence or degree of gastric damage. Thus, it does not show that, because of its fine particle size, Bayer has resulted in significantly less gastric damage than other brands of plain 5-grain aspirin.

Aspirin Content Per Tablet

663. The recommended dosage of aspirin for the relief of mild to moderate pain is one to two tablets, or 325–650 mg aspirin (Miller, Tr. 6749; CX 466, p. 35489). To measure the aspirin content of tablets, aspirin assays are conducted in laboratory analyses (Miller, Tr. 6733; Rhodes, Tr. 11643).

664. To be capable of exerting a pharmacological action, aspirin tablets must deliver a therapeutic amount of the active drug, *i.e.*, aspirin (*see generally,* Rhodes, Tr. 11372–73). This delivery consists of two aspects: absorption into the bloodstream and the amount of aspirin.

665. Well-controlled clinical trials, which have demonstrated the efficacy of aspirin as a pain reliever in comparison with a placebo, also have shown no statistically significant difference in the therapeutic response generated by less than 325 mg of aspirin versus a placebo, and by 650 mg aspirin versus 975 mg aspirin (CX 466, p. 35364).

666. The scientific literature contains reports of some brands of particular drugs containing or yielding a subtherapeutic dosage of the active moiety (*see, e.g.,* Rhodes, Tr. 11123). Such a drug product is considered "subpotent" and, as such, likely to be less efficacious than

a brand which yields a therapeutic amount (Banker, Tr. 12551). However, no witness pointed to such reports in the literature of plain 5-grain aspirin when taken in low dosages for the relief of mild to moderate pain (*see, e.g.,* Banker, Tr. 12996–13005).

667. Addressing differences of aspirin content for two tablets, Dr. Banker stated that no correlation has been scientifically demonstrated between any point in the range of 164 mg aspirin and analgesia (Moertel, Tr. 6301; Grossman, Tr. 7499–7500; Banker, Tr. 13168). Dr. Rhodes stated that no test **[163]** showed that a difference in aspirin content of 4 mg made any difference in pain relief (Rhodes, Tr. 11705).

668. In addition, Dr. Trout, an employee of respondent (CX 678, admissions 90–93) stated that he believed that 400 mg of ASA is not significantly more potent than 325 mg aspirin (Trout, Tr. 16136–44). He further stated that respondent's position in 1974 was that products containing a higher level of aspirin than Bayer did not reach the system or relieve pain more quickly than Bayer. At that time, respondent urged FDA's OTC Internal Analgesics Panel to require a disclosure stating that a higher level of aspirin per tablet did not increase effectiveness in any way (Trout, Tr. 16144–54; CX 456M). Therefore, respondent did not believe that during 1969–1974 that increases in aspirin content along the range observed in this record were significantly more potent or led to increased effectiveness.

669. To deliver a therapeutic amount of drug without inducing clinically significant side effects, aspirin tablets must not deliver an excessive or toxic amount of aspirin (*see, e.g.,* Banker, Tr. 12550–51). This concern applies to drugs with a narrow therapeutic ratio, *i.e.,* drugs for which the level of effectiveness is very close to the level of toxicity (*see generally,* Danhof, Tr. 17269; Banker, Tr. 12550–51). When taken in low dosages for the relief of mild to moderate pain, plain 5-grain aspirin does not feature a narrow therapeutic ratio (Banker, Tr. 12934, 12695).

670. No reliable scientific evidence shows that variations in aspirin content among brands of plain 5-grain aspirin have resulted in differences in analgesic effect or side effects. Therefore, comparative aspirin content data fail to provide a reliable basis for predicting the comparative therapeutic performance of plain 5-grain aspirin.

671. Aspirin is an unstable chemical entity (Rhodes, Tr. 11395–97; Winig, Tr. 14212–15). When exposed to moisture, aspirin undergoes chemical decomposition or hydrolysis. Thus exposure to moisture reduces the amount of aspirin in a tablet (Rhodes, Tr. 11641–42; Banker, Tr. 12593; Miller, Tr. 6880). Such exposure can occur when aspirin containers are opened, particularly in family bathrooms or kitchens (Rhodes, Tr. 11158, 11641; Banker, Tr. 12768).

672. Aspirin hydrolysis results in certain by-products which further the chemical breakdown or reduction in aspirin content. Thus, aspirin content tends to decrease with the passage of time (Rhodes, Tr. 11641–42; *see generally,* Wining, Tr. 14238; Miller, Tr. 6880).

673. The comparative aspirin content data in respondent's possession during the period of 1969–1974 does not show that Bayer showed a significantly superior amount of aspirin or more [**164**] consistently yields 100% of label claim (*i.e.,* 325 mg per tablet) in comparison with other brands of plain 5-grain aspirin. Respondent offered in this proceeding five reports of comparative aspirin content data, including "Commercial Aspirin Tablets" (RX 177). The investigators in RX 177 failed to control for age or conditions of storage for the tested samples and it is impossible to determine whether or not the aspirin content data reflects varying exposure to moisture through different conditions of storage or age. The investigator reported that the Bayer examples yielded the highest amounts of aspirin (RX 177). The author's failure to subject the data to statistical analysis leaves the utility of the data in doubt. The report also shows that four other brands (Kor-Val, York, Saxon, and Nasco Hygrade) yielded aspirin content figures closer to 100% of label claim than Bayer. These four brands were 1–3 mg away from 325 mg while Bayer was 5–8 mg away (RX 177).

674. Respondent also offered "Bayer Aspirin—Stability" (RX 176). This report offers no information about the comparative aspirin content of different brands of plain 5-grain aspirin. Similarly, RX 182, "A. O. Aspirin for Assay, Kress Aspirin Tablets" offers no information about the comparative aspirin content of brands of plain 5-grain aspirin.

675. RX 408 - "Supplemental Data on Bayer Aspirin" includes "Competitive Study—BA Tablets," by E. J. Mannix, a Sterling employee (January 20, 1971) (RX 408Z). In this test, the investigator conducted aspirin assays on nine brands of aspirin (RX 408Z). The investigator reported that only one other brand, (Squibb) equalled Bayer by not falling below 100% (RX 408Z). Squibb also featured more uniformity than Bayer (Rhodes, Tr. 11094–95). He also noted that one St. Joseph tablet fell below the official aspirin content limit (RX 408Z). The failure to perform a statistical analysis puts the significance of this data in doubt. In addition, the report shows that Squibb wad closer to 100% of label claim than Bayer.

676. In "Competitive Study—BA Tablets" by E. J. Mannix (March 8, 1971) (RX 408Z001–Z002), the investigator conducted aspirin assays on 25 brands of aspirin (RX 408Z011). The investigator concluded that only Bayer was at or above 100% and that eight brands (Richards, Woolworth, Norwich, Sav-On, Blue Cross, Macy's, Lit, and Masters)

yielded samples with aspirin content outside the official limits (RX 408Z012). However, the failure to perform a statistical evaluation leaves the utility of this data in doubt. In addition, only two brands (Bayer and Norwich) were represented by more than one lot (RX 408Z011). RX 408 series also included control data sheets for Bayer dated 1966 (RX 408Z042–Z045), and 1969 (RX 408Z048 and Z052). Since these reports contain aspirin content data only for Bayer, it affords no information about the comparative aspirin contents of different brands of plain 5-grain aspirin. **[165]**

677. Respondent also had comparative aspirin content data which appeared in CX 448 ("223 Study"). As discussed in greater detail hereinafter, the results of the "223 Study" are questionable because of several substantial methodological problems. In any event, the aspirin content data in RX 448 does not show that Bayer is significantly superior to all the 220 aspirin brands tested. The author reported that six brands (McKesson, Norwich, Rexall, St. Joseph, Squibb, and Walgreens) passed the same test as Bayer (CX 448Z001). Five minor brands (Acme, CB, Norco, Royal Crest, and Smart) also passed this test (CX 430B; see CX 448Z027). In addition, two brands (McKesson and St. Joseph) yielded the same average aspirin content as Bayer (CX 448Z001). Four brands (Norwich, Rexall, Squibb, and Walgreens) yielded aspirin content averages closer to 100% of label claim than Bayer (CX 448Z001). Since the investigator failed to subject these averages to statistical evaluation, the utility of this data remains in doubt.

678. With respect to "The Quality of Aspirin Tablets" (CX 445), the investigators failed to control for the test samples' age or conditions of use or storage. For aspirin content results, the investigators reported that aspirin content for all the tablets was very close to label claim (CX 445Z001). Both Bayer and Squibb contained no samples which yielded less than 100%, while McKesson, St. Joseph, Rexall, and Norwich did (CX 445Z001). In addition, 39 minor or regional brands contained no samples which yielded less than 100% (CX 445Z). In any event, the failure to test for statistical significance leaves the utility of this data in doubt.

679. With respect to the Snell Study (RX 183), the investigators failed to control for the test samples' age and conditions of use (Terry, Tr. 10970–71; Rhodes, Tr. 11670; RX 393). Thus, it is impossible to determine whether or not the aspirin content data reflects variations in age, conditions of storage or use, or the brands.

680. The investigators in RX 183 reached the following conclusions concerning aspirin content: (1) Bayer had the highest average aspirin content; (2) the other major brands had significantly lower aspirin content averages; (3) McKesson was the least uniform; and (4) Bayer

yielded the fewest number of failures (RX 183Z015). This data does not show that Bayer is statistically significantly superior to each tested brand. The difference between average aspirin content for Bayer and McKesson is not at P=.05 or better (RX 183Z016). In addition, Rexall was more uniform than Bayer (RX 183Z016). McKesson's average aspirin content was at 100% of label claim, Norwich's and St. Joseph's were 1 mg away from 100%, and Squibb's and Rexall's were 2 mg away from 100%, while Bayer's was 3 mg away from 100% (RX 183Z016). In addition, the author testified that, if the assumptions underlying his assignment of utility ratings to this data were changed, different utility ratings would **[166]** result (Terry, Tr. 10984–93). These would reward the other major brands for averaging closer to 100% of label claim than Bayer (Terry, Tr. 10984–93).

681. Respondent offered two reports of comparative aspirin content data which it acquired after 1974 (RX 187 and RX 250-Patel). However, these reports do not corroborate the proposition that Bayer yields a significantly superior amount of aspirin per tablet or more consistently yields 100% of label claim than all other brands of plain 5-grain aspirin tested. The purpose of RX 250-Patel, "GLC Analysis of Aspirin From Solid Dosage Forms," Patel, *J. Pharm. Sci.,* Vol. 61, No. 11, p. 1794 (November 1972), was to investigate differences among aspirin made by different manufacturers (RX 250-Patel, p. 1794). In this test, the investigators tested five unidentified brands of aspirin along three parameters, including aspirin content (RX 250-Patel, p. 1796). The authors broke the code used for the tested aspirin brands (RX 251). The record indicates that respondent learned the identity of the brands, including Bayer, in June 1977 (G. Goldstein, Tr. 15776). The test methodology of the Patel Study has several deficiencies: (1) inadequate information about sample size; (2) the failure to blind; and (3) the failure to subject the test data to statistical evaluation; and (4) failure to control for age and conditions of storage. The authors' conclusions centered on the use of the GLC method to make these pharmaceutical measurements (RX 250-Patel, p. 1796).

682. The failure to perform statistical evaluation leaves the utility of the Patel Study in doubt. Moreover, the data does not show that Bayer yielded more aspirin content, on the average, or more consistently yielded 100% of label claim than the other four brands. Three brands (A-C, or Bayer, Lilly, and Squibb) consistently yielded aspirin content averages over 100% (RX 250-Patel, p. 1796). Lilly and Bayer yielded exactly the same average (RX 250, Patel, p. 1796). Squibb apparently yielded an aspirin content closer to 100% than Bayer (RX 250-Patel, p. 1796). Since the author failed to perform a statistical analysis, the test results' significance remains in doubt.

683. Respondent also relies on the FDA-NCDA study I: "Semiauto-

mated Analysis of Aspirin in Bulk and Tablet Formulations and SA in Aspirin Formulations" (RX 287Z/B–Z014). The general features of RX 287 have been discussed hereinabove. In testing the accuracy and precision of a proposed aspirin assay, the investigators' purpose was to evaluate the quality of commercially available aspirin products and the adequacy of present standards (RX 287C). The investigators conducted an aspirin assay on 58 aspirin formulations representing 38 manufacturers and 34 samples of bulk aspirin from 12 manufacturers (RX 287C). The investigators failed to control for the tablets' age and conditions of use or storage, and it is **[167]** impossible to determine whether the aspirin content figures reflect variations in age, conditions of storage, or the brands. The investigators concluded that four samples failed to meet official limits (RX 287K).

684. Even if the test's limitations were disregarded, the test results do not show that Bayer yielded a statistically significantly superior amount of aspirin or more consistently yielded 100% of label claim than all the other tested brands. When subjected to statistical evaluation (RX 415 for identification) by respondent's witness, Dr. Horner, two brands (Dewey, and St. Joseph) registered means as close to 100% as Bayer yet with more uniformity than Bayer (Rhodes, Tr. 11703–04; Banker, Tr. 13124-25). All three brands yielded aspirin content of at least 100% of label claim (RX 287Y, Z004, and Z007) (Rhodes, Tr. 11703; Banker, Tr. 13124).

685. The comparative aspirin content data which respondent acquired after 1974 included RX 187, which failed to show statistical evaluation. The report does not show that Bayer yielded a statistically significantly superior amount of aspirin or more consistently yielded 100% of label claim. The other, RX 250-Patel, also did not show that Bayer was statistically significantly superior or more consistent than all other tested plain 5-grain aspirin brands. Furthermore, since this study failed to control for the tablets' age and conditions of use or storage, it is impossible to determine whether the test results reflect variations in age, in conditions of storage, or in the brands.

686. The comparative aspirin content data included in CX 445, RX 177, RX 408, RX 183 present inconsistent results and thus an inconclusive picture about Bayer's aspirin content in comparison with other brands tested. This data does not show that Bayer, when tested against brands of comparable age and conditions of storage or use, yields a significantly superior amount of aspirin or more consistently yields 100% of label claim (325 mg per tablet) than its major competitors.

687. In any event, aspirin tablet content data would not serve as a reliable basis for predicting the superior therapeutic performance of USP aspirin tablets. This record is devoid of any evidence which

shows that the content variations observed in the various studies can be expected to result in any appreciable therapeutic inequivalence when used at normal OTC dose levels. *Also see* F. 573–578, *supra.*

Free Salicylic Acid (FSA)

688. A small amount of FSA (or SA) is present in all commercially available plain 5-grain aspirin tablets, including Bayer Aspirin, as a by-product of the manufacturing process [**168**] (Rhodes, Tr. 11390–91; Banker, Tr. 12630). The USP's FSA limit for plain 5-grain aspirin tablets is .3%. The amount of SA present in aspirin tablets can be determined in laboratory tests (Miller, Tr. 6739–33; Banker, Tr. 12905).

689. FSA is an impurity in an aspirin tablet which can accelerate the decomposition process. The presence of FSA catalizes the rate of degradation of aspirin. If one brand of aspirin tablet has a higher amount of FSA at the time of manufacture, when that product is exposed to conditions of storage, the excessive amount of FSA is likely to result in more rapid decomposition. Therefore, it is possible that the product with the greater amount of FSA may fall below the legal limit for aspirin content sooner than the product with less FSA (Rhodes, Tr. 11159–60; Banker, Tr. 12630, 12685).

690. In the presence of water, aspirin hydrolizes and breaks down to form FSA and acetic acid. The most common place to store drug products is in a bathroom cabinet. The aspirin is therefore exposed to high temperature and humidity in the homes. Thus, once aspirin reaches consumers' homes, great stress is applied to it (Rhodes, Tr. 11160–61).

691. As salicylic acid increases in an aspirin tablet, dissolution rate will decline. The reliability of the dissolution rate of the tablet is also reduced (Banker, Tr. 12684–85, citing, Zoglio, M., "Pharmaceutical Heterogeneous Systems III: Inhibition of Stearate Lubricant Induced Degradation of Aspirin by Use of Certain Organic Acids," *J. Pharm. Sci.,* 57:11, 1877–1880 (July-Dec. 1968).

692. When aspirin decomposes and salicylic acid is formed, it has the capability to undergo "sublimation," forming pure crystals of salicylic acid on the surface of the tablet dosage form. Sublimation is a process by which a solid material goes into a gaseous state and then condenses out again as a solid material on another surface. Figure 1 of RX 250-Gore (1968) shows needle-like pure crystals of salicylic acid on the outside of a tablet. Thus, FSA is not necessarily uniformly distributed throughout an aspirin tablet once hydrolysis begins (Banker, Tr. 12647–49, citing Gore, "Significance of Salicylic Acid Sublimation in Stability Testing of Aspirin-Containing Solids," *J.*

Pharm. Sci., 57(11):1850 (1968); Falliers, Tr. 13307; Danhof, Tr. 17049–50).

693. It is desirable to limit the amount of FSA in an aspirin tablet because it is an erosive substance, and is contra-indicated by the USP for contact with mucous membranes. Free salicylic acid is described by the USP as an agent which is used to destroy skin tissue. It is largely a product of the decomposition of aspirin and can adversely change the physical properties of an aspirin tablet with a negative effect on its disintegration and dissolution rates. The adverse therapeutic [**169**] effect of free salicylic acid has been observed by at least one high official of the USP (Banker, Tr. 12628–33; Danhof, Tr. 17001, 17032–33; RX 218). Dr. Banker relied on RX 250-Dispensatory; RX 250-Remington, and several articles, including Morris, C., "Metabolism of Aspirin in Lumen and Corpus Tissues of Rat Stomach During First Four Minutes After Administration," *J. Pharm. Sci.*, 62(6):1017 (1973); Root, W., "Physiological Pharmacology," Vol. 1, pp. 314–19, Academic Press (1963): Salter, W., "A Textbook of Pharmacology," pp. 45–55, W. B. Saunders Co. (1952); Kelly, C., "Determination of the Decomposition of Aspirin," *J. Pharm. Sci.*, 59:1053 (1970) (Banker, Tr. 12650–51).

694. Dr. Miller admitted that the presence of .3% FSA in an aspirin tablet, acceptable under the USP standard, may lead to a chemical reaction which can produce more FSA. Thus, the amount of FSA in an aspirin tablet is an indication of how stable it will be over time.

695. Dr. Miller agreed with the statement in Salter, W., *A Textbook of Pharmacology* (p. 55), that "This irritating effect is much more marked with the free salicylic acid than it is with sodium salicylate or with acetylsalicylic acid." (Miller, Tr. 6891; Salter, W., *A Textbook of Pharmacology*, p. 55, W. B. Saunders Company (1952)).

696. The Food and Drug Administration has taken the position that increasing the amount of FSA permitted in analgesic tablets is not desirable. Thus, the Food and Drug Administration, like respondent, opposed relaxing the USP limits to permit more FSA in analgesic tablets from .1% to .3% (G. Goldstein, Tr. 14977–83; RX 168B).

697. It is generally recognized that salicylic acid is inferior to acetylsalicylic acid (aspirin) as an analgesic. Thus, to the extent that the impurity salicylic acid is increased in an aspirin tablet due to the breakdown of acetylsalicylic acid, the therapeutic effectiveness of the aspirin tablet may be reduced (G. Goldstein, Tr. 14959–60, 14965–67; Danhof, Tr. 17056; RX 168).

698. In April 1971, Dr. John sent a memo to Dr. Trout calling to his attention an animal study in which salicylic acid was found to be the causative agent in deformities in rat fetuses (John, Tr. 5647–48; RX 320).

699. *Remington's Pharmaceutical Sciences* is a recognized pharmaceutical reference book. The 13th Edition of *Remington* (1965) at p. 862 states:

> Salicylic acid is not employed internally as on the gastrointestinal tract. It is employed externally on the skin where it [170] exerts a slight antiseptic action and a marked keratolytic action. The latter property makes salicylic acid a beneficial agent in the local treatment of warts, corns, fungus infections and certain forms of eczematous deteratitis. Tissue cells swell, soften and ultimately desquamate.

(Danhof, Tr. 17033–34). Keratolytic action means the dissolving of the surface dead cells, and desquamation means the loss of these cells from the surface of the skin. Similar or identical statements appeared in the 14th Edition of *Remington* (1974) at p. 781 and the 15th Edition of Remington (1975) at p. 725 (Danhof, Tr. 17034–35).

700. Because of the erosive properties of salicylic acid, it is undesirable to have it in an aspirin tablet. The less salicylic acid in the tablet, the less likely it is to irritate the gastric lining (Danhof, Tr. 17036).

701. Salicylic acid irritates the gastric mucosa, and salicylic acid irritation is greater than the irritation caused by either sodium salicylate or acetylsalicylic acid. As stated by Salter, "A Textbook of Pharmacology" (W. B. Saunders Co. 1952) at p. 55:

> In the case of pills or pellets, the irritant effect of the drug [salicylates] may be demonstrated at the base of the pellet as it rests on the mucosa . . . . This irritating effect is much more marked with free salicylic acid then it is with sodium salicylate or acetylsalicylic acid.

702. Salicylic acid is not marketed at present for internal use because of problems of solubility. It is used only for external purposes (Moertel, Tr. 6369–70).

703. The *United States Dispensatory* (RX 250-Dispensatory (1955)) is a standard compendium issued under the authority of the United States Pharmacopeia Convention. It indicates that salicylic acid is used only for topical purposes, normally as a keratolytic agent at a concentration of about 2–3%. The *Dispensatory* indicates applications of salicylic acid in concentrations from 1–3% to treat acne and seborrhea (Rhodes, Tr. 11398–400).

704. The USPDI Update is an official publication of the United States Pharmacopeia, and provides current information relating to the U.S. Pharmacopeia (Danhof, Tr. 17040–41). The January-February 1980 USPDI Update, at p. 42, discusses salicylic acid. This update cautions against bringing salicylic acid into contact with the mucous membrane, showing general [171] acceptance in the scientific com-

munity of the irritation that salicylic acid may cause to mucous membranes (Danhof, Tr. 17041).

705. *The Physician's Desk Reference* (PDR) contains a compilation of information concerning products generally available on the market. It is a recognized reference book for physicians. *The Physician's Desk Reference* reflects numerous products containing salicylic acid to be used for keratolytic purposes associated with acne or dandruff. According to *The Physician's Desk Reference,* these products contain from 1–1/2 to 2% salicylic acid (Danhof, Tr. 17042–45).

706. The FDA's Miscellaneous External Drug Products Panel is one of the panels established by the FDA, like the Internal Analgesic Panel, to review OTC drugs (Danhof, Tr. 17045). Salicylic acid was assigned to this Panel. As part of this Panel's review of external drug products containing salicylic acid, it found:

> Salicylic acid is present as a keratolytic in OTC products at concentrations ranging from about 0.5 to 40 percent. It is said to be keratolytic at concentrations above 0.5 percent and keratoplastic below that level.

(RX 209B; Danhof, Tr. 17046).

707. Aspirin, salicylic acid, and sodium salicylate are different drugs with different drug actions. For example, only aspirin has an effect on platelet aggegation. Dr. Gerhard Levy and numerous other authors have noted that aspirin is more active as an analgesic, antirheumatic, and antipyretic than either salicylic acid or sodium salicylate. The USP lists salicylic acid only as a caustic and a keratolytic (Banker, Tr. 12638–47; RX 168).

708. *The Merck Index* is a standard pharmaceutical reference that describes structural formulas, chemical compositions and major chemical properties for all major drugs used in this country and around the world. It indicates the extent of solubility of drug substances in water or other media. The question of the chemical nature of salicylic acid as compared to sodium salicylate and aspirin in the stomach is a function not only of whether it is in the ionized or un-ionized state and whether it is an acid or a salt, but is also a function of the solubility and solubility rate. For example, it takes about a pint of water to dissolve one gram of salicylic acid. It would have less solubility in an acid medium like gastric fluid. It would take approximately a liter of gastric fluid to dissolve a gram of salicylic acid. Sodium salicylate has a solubility of one gram in less than one milliliter of water, and the solubility of sodium salicylate in gastric fluid would be equally high. Therefore, sodium salicylate will dissolve in [172] roughly 1/1000th of the volume of water required to dissolve

an equivalent amount of salicylic acid. It is very soluble in gastric fluid (Banker, Tr. 12660–63).

709. Both complaint counsel's witness, Dr. Orville Miller, and respondent's expert, Dr. Danhof, agreed that taking an aspirin tablet with a glass of water does not guarantee that all the salicylic acid that might be in the tablet would be dissolved immediately upon entering the stomach (Miller, Tr. 7152; Danhof, Tr. 17056–57).

710. Salicylic acid is more irritating than aspirin or sodium salicylate and is more of an irritant to the gastric mucosa than aspirin (Rhodes, Tr. 11404, citing, Salter, W., "A Textbook of Pharmacology," pp. 45–55, W. B. Saunders Co. (1952); Banker, Tr. 12638; Danhof, Tr. 17057–58).

711. The fact that sodium salicylate is more of an irritant than acetysalicylic acid has been reported in numerous scientific journals and treatises (Danhof, Tr. 17058). For example, in *Dixon, The Salicylates* (Little Brown & Company, 1963), at p. 6, there is a discussion of "significant factors in the history of aspirin." It states:

> However, sodium salicylate possessed certain unpleasant side effects, notably gastric disturbance, whilst many patients developed a strong aversion to the taste. The scene was therefore set for introduction of a derivative which might be free of these disadvantages. Aspirin was then developed as a substitute for sodium salicylate to alleviate the problem of irritation.

(Danhof, Tr. 17058–59).

712. Dr. Gerhard Levy, an eminent pharmaceutical scientist, has concluded that aspirin is a more effective analgesic than salicylic acid. Complaint counsel's witnesses agreed with this proposition. FSA also has an unpleasant taste (Moertel, Tr. 6366–67; Grossman, Tr. 7502; Banker, Tr. 12697–98; Danhof, Tr. 17056; RX 250-Levy - "Absorption" (1965); RX 168).

713. An article by Thompkins, L., "Comparison of the Analgesic Effects of Isoteric Variations of Salicylic Acid in Aspirin (Acetylsalicylic acid)," *J. Pharm. Sci.*, 65(5):760 (1975) confirms the principals set forth in RX 168, *i.e.*, that acetylsalicylic is superior to salicylic in effectiveness (G. Goldstein, Tr. 14959–60, 14965–67, 14970–71).

714. Dr. Miller's position on the acceptability of aspirin tablets containing up to 3.5% FSA is in conflict with USP standards (0.3%). **[173]**

715. Dr. Moertel testified that he would accept a level of ten times the USP standard in 1970 for FSA in plain aspirin tablets. He testified that, "Knowledgeable people in the USP would agree with my statement with regard to therapeutic safety and effectiveness." He stated that the USP standards were designed to see that consumers got a reasonable amount of aspirin, and were not related to safety or effec-

tiveness. As a member of the USP Revision Committee, Dr. Banker testified that Dr. Moertel's statement was incorrect, and was based upon his belief that salicylic acid performs in the same manner as sodium salicylate in the stomach (Moertel, Tr. 6475–77; Banker, Tr. 12672–74).

716. Dr. Banker testified that Dr. Morton Grossman's testimony, that FSA should not be a criterion for the selection of a drug product, because it is not harmful and that he would accept an aspirin tablet with 4.4% FSA, is incorrect, because it also overlooks the deleterious pharmaceutical and therapeutic effects of FSA. Dr. Banker's opinion is based upon his experience as a member of the USP Revision Committee, and upon the USP dispensing information which specifically contraindicates FSA coming in contact with mucous membranes (Grossman, Tr. 7537; Banker, Tr. 12678–79).

717. Recommended dosages of plain 5-grain aspirin can also cause adverse reactions in some people. One theory advanced in this proceeding is that salicylic acid (SA) rather than aspirin causes local gastrointestinal damage associated with aspirin ingestion. In support of this theory, respondent's witnesses (*e.g.,* Dr. Rhodes and Dr. Danhof) relied on the use of SA in external medications for removing certain skin tissues, such as acne treatments and corn removers (Rhodes, Tr. 11398–406). When so used, SA is a "keratolytic" agent because it acts on a substance in the skin known as kerotin (Grossman, Tr. 7541–44; Rhodes, Tr. 11653). Since the stomach lining contains no kerotin (Rhodes, Tr. 11653), SA does not act as a keratolytic agent in the stomach. Additionally, such external medications contain SA in higher concentrations, *e.g.,* 2.0–5.0% (Miller, Tr. 6886; Rhodes, Tr. 11652; see also, Danhof, Tr. 17219, 17210), or at levels much higher than those commonly found in aspirin tablets.

718. SA is considered an impurity in aspirin tablets (Miller, Tr. 6876; Rhodes, Tr. 11158). A substance which is an "impurity," while undesirable, is not necessarily a harmful or toxic agent (Miller, Tr. 7020; Rhodes, Tr. 11158–62). All commercially available aspirin tablets, including Bayer, contain some SA. After ingestion, some hydrolysis of aspirin occurs in the stomach and thereby exposes the stomach to additional SA (Rhodes, Tr. 11655–56; Banker, Tr. 12587).

719. Addressing variations in SA level among aspirin brands, along the range of .2–2.0 mg SA for two tablets, [**174**] respondent's witnesses, Drs. Banker and Danhof, stated that no correlation had been demonstrated between any point in this range and the incidence or degree of side effects associated with aspirin ingestion (Banker, Tr. 13065–66; Danhof, Tr. 17220–21, 17210; *see also* Grossman, Tr. 7504). Another witness for respondent, Dr. Rhodes, stated that no correlation existed between varying SA amounts in aspirin tablets and the

incidence or degree of side effects (Rhodes, Tr. 11660–62). He added that no correlation existed between various aspirin brands and the amount of gastric side effects (Rhodes, Tr. 11683). Dr. Danhof stated that his opinion about the local irritant effects of SA on the gastric mucosa was not based on comparative data for different brands of plain 5-grain aspirin (Danhof, Tr. 17210).

720. Respondent's witnesses, *e.g.,* Dr. Rhodes and Dr. Banker, relied on the potential for "sublimation" created by the presence of SA in aspirin tablets (Rhodes, Tr. 11395–97; Banker, Tr. 12647-48). However, sublimation can occur with any brand of aspirin (Banker, Tr. 13068–70). The scientific literature does not contain reports of some brands of plain 5-grain aspirin showing a higher incidence of SA crystals than other brands (Banker, Tr. 13068–70).

721. Dr. Danhof also relied on animal experiments in which he measured the relative frequency and degree of injury to dogs' gastric mucosa from a variety of salicylates, including aspirin and SA (RX 167). As discussed hereinabove, these experiments are insufficient to support a firm conclusion in humans. In addition, Dr. Danhof relied on observations, not investigations or experiments, that topical applications of SA on the mouth's mucous membrane produced caustic burns (Danhof, Tr. 17217, 17219). Dr. Danhof added that these topical applications might have featured a concentration of SA higher than that commonly found in 5-grain aspirin tablets (Danhof, Tr. 17219).

722. In addition, Dr. Danhof did not take into consideration two recently published reports which suggest that aspirin may be more injurious to gastric mucosa than SA, "Anomylous Biological Effects of Salicylates and Prostoglandins," E. M. Glenn, M.D., *Agents and Actions,* Vol. 9 (1979) (Danhof, Tr. 17201–02; CX 763 for identification); and "Selective Inhibition of Prostagland in Production in Inflammatory Exudates and Gastric Mucosa," B. J. B. Whittle, M.D., *Nature,* Vol. 284, pp. 271–83 (1980) (CX 752 for identification; Danhof, Tr. 17203). The Whittle article appeared in a respected, peer-reviewed scientific journal (Rhodes, Tr. 11090; Danhof, Tr. 17204).

723. The Glenn study compared the effects in rats of oral administration of aspirin and SA at varying dosage levels (Danhof, Tr. 17208). The use of rate is generally accepted as a good predictor of drugs which affect functions of the stomach **[175]** (Danhof, Tr. 17205–06). Rats have been used for detecting effects of anti-ulcer drugs (Danhof, Tr. 17205–06). The investigators reported that aspirin at dosage levels of 25 mg, 104 mg, and 208 mg per kilogram produced ulcers, while at higher dosage levels of 104 mg-416 mg per kilogram, SA produced no ulcers (Danhof, Tr. 17208). When aspirin and SA were compared at the dosage level of 104 mg per kilogram, aspirin produced ulcers in 5 out of 5 rats and SA produced no ulcers (Danhof, Tr. 17211). At the

low dosage of 25 mg aspirin per kilogram, 2 of 5 rats developed ulcers (Danhof, Tr. 17212).

724. The Whittle study tested the effects of sodium salicylate on the gastric mucosa of rats (Danhof, Tr. 17208). The investigator found that sodium salicylate produced far less gastric erosion that some other tested agents (Danhof, Tr. 17208). Furthermore, both investigators reported that SA, unlike aspirin, does not inhibit the synthesis of prostaglandins (Danhof, Tr. 17207). This synthesis is instrumental in protecting the gastric mucosa from irrigation (Danhof, Tr. 17207). Dr. Danhof agreed with this finding (Danhof, Tr. 17207, 17216) and the finding that an inverse relationship exists between a salicylate's activity as an inhibitor of prostoglandins and as an erosive agent (Danhof, Tr. 17208).

725. Dr. Danhof agreed that he was unable to cite any objective measurements in humans comparing the relative erosive effects of aspirin and of SA, at levels commonly found in plain 5-grain aspirin (Danhof, Tr. 17216–17). Upon cross-examination on this point (Danhof, Tr. 17210–18), Dr. Danhof qualified his opinion to be one that SA was at least as corrosive as aspirin (Danhof, Tr. 17218).

726. During 1960–1970, M. E. Auerbach, an employee of respondent, served on the USP Revision Committee (RX 286T). Mr. Auerbach was invited to this position based on his expertise in chemical analyses (RX 286X). He also was invited to serve as advisor to the National Formulary and to a World Health Organization committee responsible for revising the International Pharmacopoeia based on his expertise (RX 286Y). A Sterling employee of 41 years, he retired after serving as Assistant Director of Chemical Research and as supervisor of the SWRI analytical laboratory (RX 286).

727. In a February 18, 1969 communication to Dr. L. C. Miller, Director of the USP Revision Committee (RX 286F), on SWRI memorandum paper, Mr. Auerbach stated, "I believe you will agree that salicylic acid and its simple salts are analgetic, although less potent than aspirin . . ." (CX 435B). Respondent knew about this communication through its medical spokesman (RX 285Z001; CX 435A, C), Dr. Theodore Klumpp (RX 285L), and disagreed with this view (RX 285Z026). Respondent has admitted that SA has analgesic properties (CX 678, #792). **[176]**

728. In the same communication, Mr. Auerbach also stated, "[F]ree salicylic acid is different from many of the drug impurities treated in the compendia, in that no one is concerned about either its toxicity or pharmacology." (CX 435A). " . . . [S]alicylic acid is not more toxic or irritant than aspirin (and perhaps less so)." (CX 435B). Respondent knew about the communication of these opinions through Dr. Klumpp (CX 435A and C; RX 285Z001) and disagreed with these opinions (RX

285Z026). CX 435 also shows that Dr. Klumpp knew that conflicting opinions and evidence existed concerning the clinical significance, if any, of allowing an increase in FSA levels in aspirin tablets (RX 285Z026).

729. In a February 27, 1969 communication to Dr. L. Miller (CX 434), D. E. Guttman, a member of the USP Revision Committee (RX 286F) commented on Auerbach's opinions. Dr. Guttman was a respected scientist (Rhodes, Tr. 11394). Respondent's witness, Dr. Rhodes, has relied on one of his publications for a theory advanced concerning SA (Rhodes, Tr. 11393–94). In this communication, Dr. Guttman characterized SA as a foreigner in aspirin tablets and stated:

> I agree with Dr. Auerbach that, in the case of aspirin tablets, the undesirability of a "foreigner" does not have a pharmacological or toxicological basis but that the level of non-aspirin salicylate can be assumed to be an indicator of good manufacturing practice, or good formulation practice. CX 434A.

Respondent possessed a copy of this communication (CX 434A).

730. During 1971–1974, the Medical Director of Glenbrook Laboratories knew of no clinical evidence supporting a causal relationship between amounts of SA in commercially available plain 5-grain aspirin and gastrointestinal distress (John, Tr. 5555; *see also* Trout, Tr. 16167–70). No clinical trials have established a correlation between varying FSA levels, as found in the "223 Study," and differences in therapeutic response to aspirin tablets (John, Tr. 5566). He and Dr. Blackmore, head of SWRI, concluded that it was improbable that clinical trials would show a clinically significant difference between Bayer's FSA level and its worst competitor's level as found in CX 448 (John, Tr. 5565). In addition, Dr. John believed that aspirin was injurious to the stomach, not the SA found in aspirin tablets (John, Tr. 5612).

731. Several employees of respondent, including Drs. Tainter, Klumpp, and Marcelli, co-authored a book, *Aspirin in Modern Therapy* (1969) (Marcelli, Tr. 17659–61). Respondent published and distributed the book for no fee to physicians in this country (Marcelli, Tr. 17659–61). In the book's chapter addressing gastrointestinal reactions to aspirin ingestion, no **[177]** reference appears concerning SA as a cause of or contributor to these reactions (Marcelli, Tr. 17661–70).

732. Respondent relies on FSA data in the Snell Study (RX 183). The author reported that Bayer, St. Joseph, and Rexall yielded, on the average, 0.05% FSA, Norwich and Squibb yielded 0.05%, and McKesson yielded 0.07% FSA (RX 183Z018) and added that Norwich, Squibb, and McKesson were statistically significantly different from Bayer (RX 183Z018). Employing one FSA limit, Bayer had the lowest

failure rate and Norwich had the highest failure rate of the major brands (RX 183Z018).

733. In the "223 Study" (CX 448) discussed in greater detail hereinafter, the author reported that Bayer yielded the lowest amount of FSA, at 0.028%. The other major brands yielded average FSA levels from 0.048% (Rexall) to 0.111% (Walgreen's) (CX 448Z002). Even if this test's inadequacies were disregarded, the failure to test the FSA level data for statistical significance leaves the utility of this data in doubt. However, examination of various brands' failure rates, according to one FSA limit, shows that Bayer was not superior to the other 220 tested brands of aspirin. One major brand (Parke-Davis) and one minor brand (Safeway) yielded no failures according to this limit while Bayer yielded one (CX 430A and B; *see* CX 448Z003 and Z027).

734. Respondent relies on three reports of comparative FSA level data which it acquired after 1974 (RX 287, RX 250-Patel, and RX 216). However, these reports do not corroborate the proposition that Bayer yields a significantly lower FSA level than all other brands of OTC plain 5-grain aspirin. In RX 250-Patel, the data does not show that Bayer yielded the lowest FSA level. Bayer's range was 0.04 (one sample) — 0.05% (two samples) while St. Joseph's range was "traces" (three samples) — 0.05% (one sample) (RX 250-Patel, p. 1796).

735. RX 216 is a set of reports, obtained from Norwich, which contain comparative FSA level data. The purpose of these reports was to compare the physical and chemical stability of Norwich and Bayer, when stored in Bayer's clear polystyrene bottle and when stored in flint glass bottles (RX 216A). In the first part (RX 216A–B), the investigators measured FSA levels for both brands' samples in flint glass bottles stored at room temperature, in Bayer's polystyrene bottle stored for two months at elevated temperature, and in flint glass bottles stored for two months at the same elevated temperature (RX 216B). In the second part (RX 216C–F), the investigators measured FSA levels for both brands, represented by samples from both containers, some of which were stored at room temperature, and some at two types of elevated temperature (RX 216C and E).

736. In the first test (RX 216A and B), the investigators reported that all three Bayer samples registered 0.01% FSA while [178] two Norwich samples registered 0.05% and one registered 0.06% FSA (RX 216B). In the second test (RX 216C–F), the investigators reported that Bayer's samples registered FSA levels from 0.02%–0.04% (RX 216D) and Norwich's samples registered FSA levels from 0.05%–0.08% (RX 216F). Even if these tests' inadequacies were disregarded, the failure to perform a statistical analysis leaves this data's utility in doubt.

737. RX 287 (FDA-NCDA Aspirin Survey) contains two FSA studies: "Aspirin—A National Survey I: Semiautomated Analysis of Aspirin

in Bulk and Tablet Formulations and SA in Aspirin Formulations" (RX 287A/B Z012) and "Aspirin—A National Survey II: Determination of SA in Bulk Aspirin and Aspirin Formulations by High-Pressure Liquid Chromatography Using a Flourescence Detector" (RX 286Z015–Z026).

738. In "National Survey I," the investigators used a proposed method to measure SA levels of 58 formulations representing 38 manufacturers and 34 bulk aspirin samples from 12 manufacturers (RX 287C). The investigators reported that the proposed method was satisfactory for use as an official test and that its results generally were higher than those generated by the official procedure (RX 287K). They also reported that 18 tablet samples failed to meet the official SA limit (RX 287K).

739. When subjected to statistical evaluation (RX 415 for identification) by respondent's witness, Dr. Horner, three brands (St. Joseph, Lilly and Davis) registered lower FSA levels and more uniformity than Bayer (Rhodes, Tr. 11675–77). Dr. Banker stated that the greatest difference existed between St. Joseph and Bayer and that Lilly and Davis were statistically insignificantly different from Bayer (Banker, Tr. 13124–25). Bayer registered an FSA level statistically significantly lower than only two of 16 other manufacturers (Horner, Tr. 10860).

740. In "National Survey II," the investigators' purpose was to test another proposed method for measuring SA (RX 287Z016). They measured SA levels in 34 bulk aspirin and 50 tablet formulations (RX 287Z017). The investigators' conclusions centered on the use of the proposed method in comparison with those SA test methods used in "National Survey I" (RX 287Z019–Z021). The authors did not perform a statistical analysis of the results. Using this procedure, Bayer registered a lower FSA level than the other three tested 5-grain aspirin brands (Marshall, Norwich, and Stanback) (RX 287Z025).

741. The comparative FSA level data which respondent obtained after 1974 included three reports (RX 250-Patel; RX 216; RX 287Z015-Z026) which failed to include statistical evaluations. Thus, these reports do not show that Bayer yields a statistically significantly lower FSA level than the other tested aspirin brands. The other post-1974 comparative data also did not show Bayer produced a statistically significantly [179] lower FSA level than at least 17 other brands of 5-grain aspirin. Three brands (Davis, St. Joseph and Lilly) registered lower FSA levels than Bayer. Eleven other brands registered FSA levels statistically insignificantly different from Bayer's. Three brands (St. Joseph, Lilly, and Cord) produced FSA levels more uniformly than Bayer. Since this study failed to control for the tablets' age and conditions of use or storage, it is impossible to determine

whether the differences reflect variations in age, conditions of storage, or the brands.

742. The comparative FSA level data reviewed hereinabove present inconsistent results and thus an inconclusive picture about Bayer's FSA level in comparison with that for 220 brands of plain 5-grain aspirin. This data does not show that Bayer, when tested against brands of comparable age and conditions of storage or use, yields a significantly lower amount of FSA than major competitors.

743. There is no dispute in this record that it is desirable, consistent with economic and technological limitations, to keep the FSA level as low as possible in aspirin tablets. By repeated recrystalization, for example, it is possible virtually to eliminate FSA from aspirin tablets at the time of manufacture.

744. The record as a whole also suggests that over the years Sterling has implemented non-aqueous manufacturing process and high quality control procedures aimed at maintaining an FSA level much lower than the USP standards and has been largely successful in that regard. The record is not clear as to the statistical significance of the differences observed in the various studies. The record is clear, however, that the magnitude of differences observed is insufficient to support a conclusion that Bayer Aspirin is therapeutically superior in significant respects to all other aspirin brands.

Tablet Stability

745. It is recognized that stability is a desirable attribute in aspirin tablets. Aspirin is very sensitive to hydrolysis. Water attacks the drug molecule and splits it into FSA and acetic acid. This process can be undesirable because the active drug is deteriorating and can advance to the point where the drug no longer meets USP standards. FSA is also an irritant to the gastric mucosa, and is undesirable to have it present in a tablet designed for oral use. Aspirin hydrolysis occurs rapidly and easily. Therefore, in formulating an aspirin tablet, the manufacturer needs to take care to reduce this problem of stability to a minimum (Rhodes, Tr. 11170–71; Banker, Tr. 12770–71).

746. It is desirable that a drug product be of acceptable quality after production as well as at the end of its shelf [180] life. Shelf life is the period which the FDA assigns to drug products. If the product is stored appropriately, it is expected to retain therapeutic efficacy up until the end of the shelf life period. Because aspirin is highly liable to hydrolysis, and because conditions such as an increase in temperature or humidity affect hydrolysis, the formulation and production of aspirin must involve substantial attention to the stability of the product (Rhodes, Tr. 11170–71; Banker, Tr. 12592–95).

747. Stability is a particularly important characteristic in a product

that may sit on a shelf for a long period of time and be used only from time to time (Winig, Tr. 14287–89; Feinstein, Tr. 16491). The expiration date for Bayer Aspirin is 10 years while the expiration date for other USP aspirins is 5 years.

Purity

748. It is generally accepted that, as in all drug products, it is desirable to have the least amount of impurity in an aspirin tablet (G. Goldstein, Tr. 14851).

749. Since many substances can cause allergic reactions in humans, it is desirable that a drug product be as pure as possible. Generally speaking, a drug with impurities is more likely to cause an adverse reaction than a pure one. The larger the quantity of impurities, the greater the chance that someone will develop an allergic reaction (Falliers, Tr. 13272).

750. Conjugation means that molecules have combined with protein. *In vitro* conjugates are more likely to cause allergic reaction. Although a small molecule by itself will not produce one, a larger combination will. Protein by itself may not be recognized as a foreign matter, but the attached molecule makes it foreign and a person may become allergic to even his own protein. For certain chemicals, conjugation must occur before a consumer can have an adverse reaction caused by a substance (Falliers, Tr. 13341).

751. The animal study by DeWeck, A., entitled "Immunological Effects of Aspirin Anhydride, A Contaminant of Commercial Acetylsalicylic Acid Preparations," *Internat. Arch. Allergy Applied Immun.*, 41:393, 401 (1971) suggested that aspirin anhydride conjugated, but pure aspirin did not. DeWeck's study indicated that animals had an allergic reaction to aspirin anhydride that they did not have to pure aspirin. The study also suggests that aspirin anhydride is an immunogen, *i.e.*, it produces antibodies, which is a prerequisite for producing analgesic reactions. A substance which produces antibodies will produce some allergic reactions in persons. In [181] order to have a true allergy, an antibody must be formed. DeWeck suggested that pure acetylsalicylic acid or pure aspirin samples appeared to be nonimmunogenic (Falliers, Tr. 13344–45).

752. The animal work of Dr. DeWeck suggested that extremely small amounts of aspirin anhydride can cause adverse reactions. The presence of as little as 5 to 50 millionths of a gram of aspirin anhydride in two aspirin tablets, the normal dosage, can give rise to sensitivity. This is the equivalent of from .001 to .01% of a gram of aspirin (Rhodes, Tr. 11538–43; Banker, Tr. 12088, 12801–02; Falliers, Tr. 13335, 13346).

753. The amount of aspirin anhydride varies among various brands

of aspirin tablets (Falliers, Tr. 13339-40, 13358–59). According to Dr. Falliers, a number of brands of aspirin have been found to have amounts of aspirin anhydride in excess of the amounts noted above (Falliers, Tr. 13358; RX 175).

754. Dr. DeWeck suggested that the presence of aspirin anhydride in an aspirin tablet:

> Represents a potential hazard to health and may be responsible for some of the untoward reactions to aspirin. Accordingly, controls on the level of aspirin anhydride present in ASA [aspirin] preparations and fabrication procedures susceptible to minimize aspirin anhydride contamination should be fostered (Falliers, Tr. 13346–47; DeWeck, "Immunological Effects of Aspirin Anhydride, A Contaminant of Commercial Acetylsalicylic Acid Preparations," *Internat. Arch. Allergy Applied Immun.,* 41:393 (1971) at pp. 415–16).

Dr. Falliers agrees with the conclusion of Dr. DeWeck (Falliers, Tr. 13346).

755. The article by Bundgaard, H., "Acetylsalicylsalicylic Acid: A Potentially Immunogenic Impurity in Acetylsalicylic Acid," *J. Pharm. Pharmacol.,* 26:18–22 (Jan. 1974) states that the work by DeWeck "strongly suggests that the sensitizing effect is due to an impurity and not to the ASA itself." Dr. Bundgaard's own research confirmed the presence of aspirin anhydride as an impurity (*see* p. 21). Bundgaard agrees that aspirin anhydride is a potent immunogen (Falliers, Tr. 13360–61).

756. The published animal research of Drs. DeWeck and Bundgaard relating to aspirin anhydride are sufficient to make a reasonable medical judgment that aspirin anhydride may be an undesirable impurity in aspirin tablets.

757. Acetylsalicylsalicylic acid ("ASSA") is also an aspirin impurity. ASSA is "able to react with protein model **[182]** amino compounds with the formation of N-salicyloyl protein amines. ASSA conjugates with a protein molecule, forming a potent immunogen." (Falliers, Tr. 13361–62, citing Bundgaard at 22).

758. A third impurity which may be the cause of aspirin sensitivity is salicylisalicylic ("SSA"), a derivative of acetylsalicylsalicylic acid (Falliers, Tr. 13365).

759. Dr. Bundgaard's animal study, "Role of Amino-Reactive Impurities in Acetylsalicylic Acid Allergy," *Int. Arch. Allergy Appl. Immunol.,* 49 (1–2):119–24 (1975) is an article published in an authoritative journal. As the article suggests, all three impurities—ASSA, ASAN, and SSA—appear to induce contact sensitivity and antibody formation in animals. Aspirin that had no impurities failed to produce antibody formation. The article concludes that ASAN and ASSA are "two very commonly occurring impurities in commercial

ASA preparations and that these are capable of inducing the formation of salicyloyl-7 antibodies in experimental animals. Dr. Falliers testified that these animal data provide a reasonable foundation to make a medical judgment that an aspirin tablet with less ASAN and ASSA would be preferable to one having those impurities in larger amounts (Falliers, Tr. 13367–68).

760. Complaint counsel's witness, Dr. Grossman, and respondent's expert witness, Dr. Danhof, agree that "in general, pure drugs are preferred to less pure drugs." (Grossman, Tr. 7358; Danhof, Tr. 17048). However, no witness identified a correlation between varying amounts of SSA in aspirin tablets and varying hypersensitivity experienced by people (*see, e.g.,* Rhodes, Tr. 11623, 11684; Falliers, Tr. 13334–36, 13340–45, 13523–26).

761. There are scientific articles discussing an impurity causing an adverse reaction to a drug product rather than the drug (Falliers, Tr. 13273–77). An example is penicillin (Falliers, Tr. 13275–76). One scientific article discussing penicillin is (proposed) RX 328, "Generic Terminology and the Cost of Drugs," published in the *Journal of the American Medical Association,* p. 80 (July 1969), authored by Dr. Dale Friend of Harvard University (Falliers, Tr. 13274–75). An adverse reaction to penicillin in many persons was found to be caused by a small amount of impurity and not by the penicillin. When the impurity was removed, there was no adverse reaction in these patients (Falliers, Tr. 13275–77). The penicillin given to the patients in the study reported by Friend met USP standards, yet adverse reactions to impurities occurred (Falliers, Tr. 13273–78). Impurities in penicillin are a clear example of the desirability of manufacturing as pure a drug product as possible (Rhodes, Tr. 11286–87; Falliers, Tr. 13272).

762. The AMA Council on Drugs is a council appointed by the American Medical Association to express expert opinion on the [183] safety and efficacy of drugs. The Council maintains a *Registry of Adverse Reactions* which compiles reports from medical practitioners of types of adverse reactions of drugs. As reported by the Council in an article published in the *Journal of the American Medical Association,* and as set forth on their form for reporting adverse reactions, among the factors recognized to contribute to adverse reactions are "contamination of drug," "decomposition of drug," "improper identifying or precautionary labeling." (Falliers, Tr. 13294–95, 13299–300; RX 250-AMA Council on Drugs, "Registry of Adverse Reactions," *JAMA,* Vol. 188, No. 4, p. 374 (1964)).

763. However, the clinical significance of the presence of varying amounts of these impurities in humans has not been scientifically demonstrated and is disputed. In a 1978 publication appearing in a reputable journal (Rhodes, Tr. 11089), the authors reviewed investiga-

tions and literature from 1971–1977 and concluded that ASAN and ASSA, as detected *in vitro* and animal tests, has no clinical significance in humans (Rhodes, Tr. 11620). After considering this article, a witness for respondent agreed that " . . . the case against ASAN is unproved." (Rhodes, Tr. 11623).

764. No witness in this proceeding testified to a correlation between varying levels of ASAN, ASSA or SSA and varying incidence or degree of hypersensitivity in human subjects. In the same article discussed above, the authors concluded that no correlation existed between varying amounts of ASAN and ASSA and varying degree or incidence of hypersensitivity in human subjects (Rhodes, Tr. 11623; *see also,* Grossman 7585, 7525–30).

765. The animal studies of Drs. DeWeck and Bundgaard made no attempt to correlate varying amounts of these aspirin impurities, as found in aspirin tablets commercially available in this country, with varying hypersensitivity as experienced by humans (Falliers, Tr. 13340–45, 13523–26). Dr. DeWeck explicitly stated in his article that further work involving humans would be necessary (Falliers, Tr. 13523–26).

766. On the other hand, during 1971–1974, the medical director for Glenbrook was skeptical about the clinical relevance of the animal research by DeWeck and Bundgaard (John, Tr. 5653). He was unaware of any human studies following up Dr. DeWeck's 1971 research (John, Tr. 5652) and believed that respondent would have substantiated Dr. DeWeck's research if it had been possible (John, Tr. 5693). At the time he brought an asthma expert to a meeting of the FDA Internal OTC Analgesics Panel in 1974, he would have expected to know of any such followup studies (John, Tr. 5652).

767. Even if the data on ASSA, ASAN, and SSA levels were accepted at face value, the sketchy comparative data in **[184]** respondent's possession during 1969–1974 does not show that Bayer had statistically significantly lower levels of these impurities than other brands of plain 5-grain aspirin. Respondent offered a set of reports in RX 175, including "Detection of ASAN in Aspirin by TLC," by A. Crain, a Sterling employee (September 3, 1971) (RX 175A and B). The purpose of this test was to detect and estimate ASAN in aspirin powder at low levels, by a new procedure (RX 175A). The investigator tested six samples of Bayer Aspirin crystals, one sample of a Monsanto crystal, and one sample of a Dow crystal (RX 175B). This record indicates that RX 175A–B is merely exploratory and unreliable for several reasons: (1) an inadequate number of samples (Rhodes, Tr. 11478); (2) no information about the investigator's qualifications; and (3) the failure to subject the results to statistical evaluation. In any event, the data did not show that Bayer yielded the lowest amount of ASAN. The Bayer

crystals yielded less than 20 parts per million ("ppm"), Monsanto 10–20 ppm, and Dow about 20 ppm (RX 175B; Banker, Tr. 12979). Because of the failure to perform a statistical analysis, the utility of this data remains in doubt. In addition, the author noted that the analytical error was approximately of the order of 40–50% (RX 175A).

768. RX 175 also included another exploratory study, "Determination of ASAN in Commercial 5 Grain Aspirin Tablets," by A. Crain (June 6, 1972) (RX 175C and D). The purpose of this test was to measure ASAN levels with a different, more precise test procedure (RX 175D). The authors conducted this test on 12 brands of aspirin (RX 175C). RX 175 is unreliable for the same reasons discussed with respect to the aspirin powder study. At any rate, the data do not show that Bayer registered a lower ASAN level than the other 11 brands. On the average, St. Joseph registered less ASAN than Bayer (RX 175C; Banker, Tr. 12970). McKesson and Korvettes also registered lower ASAN levels than Bayer (RX 175C; Banker, Tr. 12971). Because of the failure to perform a statistical evaluation, the utility of the test results remains in doubt.

769. RX 175 also included, "ASAN; Statistical Evaluation of Results," by A. Crain (August 1, 1972) (RX 175E and F). In this report, the investigator reviewed the results of the two studies in RX 175 discussed above, and conducted a reanalysis of the old data for ASAN levels of 46 of these 48 samples, and the absolute difference between the results of the two analyses for each brand (RX 175E), and reported that a difference in values of 18 ppm could be considered significantly different (RX 175F).

770. This reanalysis is unreliable for the same reasons discussed with respect to earlier reports in RX 175. While the author offered a guideline for statistically significant differences, the level of significance is not stated. Additionally, one missing sample was a Bayer sample which [185] registered a high value of "12" and the other missing sample was a St. Joseph sample which registered a low value of "7" (RX 175F and C, respectively). However, applying the author's own guideline does not show that Bayer yielded a significantly lower ASAN level than the other 15 brands (RX 175E and F). In this context, Bayer is statistically insignificantly different from five brands (St. Joseph, Grand Union, Rexall, McKesson, and Quali Craft) in the reanalysis results reported in Column II (RX 175E and F). In the first analysis, whose results are reported under Column I, Bayer is statistically insignificantly different from six brands (St. Joseph, Grand Union, Rexall, McKesson, Quali Craft, and Korvettes) (RX 175E and F). However, the author did not apply this guideline and report that statistically significant differences existed among the brands (RX 175F; Banker, Tr. 12972–74).

771. RX 175 also included "Determination of ASAN in Commercial Five-Grain Aspirin Tablets," by C. E. Joseph, a Sterling employee (June 29, 1972) (RX 175G), where the investigator reported the results of measuring ASAN on samples of six brands (RX 175G). Since this report includes no information on Bayer samples, it is impossible to draw any conclusion from this report concerning whether Bayer yields a significantly lower level of ASAN than other brands of plain 5-grain aspirin.

772. Thus, during 1969–1974, respondent had three reports of test (RX 175) comparing Bayer with 15 plain 5-grain aspirin brands, including five major brands (St. Joseph, Squibb, Rexall, Norwich, and McKesson) in terms of levels of ASAN, and one report of comparative ASAN level data which contained no information on Bayer. RX 175 does not support a conclusion about whether Bayer yields a significantly lower ASAN level than other plain 5-grain aspirin brands.

773. During 1969–1974, respondent had no reports of tests comparing Bayer with any other brand of plain 5-grain aspirin in terms of levels of ASSA or SSA.

774. Respondent offered two reports of comparative data concerning levels of impurities which it acquired after 1974 (RX 287 and RX 250-Patel). However, these reports do not support the proposition that Bayer yields a significantly lower level of ASAN, ASSA, or SSA than other brands of plain 5-grain aspirin. In the Patel Study, the authors reported that Bayer yielded "traces" of ASSA while the other four brands yielded amounts susceptible to measurement (RX 250-Patel, p. 1796). The authors' failure to perform a statistical analysis leaves the test results' utility in doubt.

775. In the FDA-NCDA Study of aspirin impurities, "Aspirin—A National Survey III: Determination of Impurities in Bulk Aspirin and Aspirin Formulations by High Pressure Liquid [**186**] Chromatography and Spectrophotometric Procedures" (RX 287Z027–Z052), the purpose of this exploratory test was to assess a testing method for detecting and measuring impurities in 1972 tablets representing 33 manufacturers and 34 bulk aspirin samples representing 12 bulk suppliers (RX 287Z028). The investigators found: (1) additional, but unspecified impurities; (2) the test method was successful for measuring ASAN; (3) SSA is a commonly occurring impurity in commercial aspirin preparations; (4) generally the ASSA levels were lower in bulk aspirin than in the derivative aspirin tablets (RX 287Z028, Z030–Z032). The test data show that Bayer, in tablet form and in bulk, did not yield the lowest level for ASAN, ASSA, or SSA (Miller, Tr. 6805–06; Rhodes, Tr. 11633–40; *see also,* Horner, Tr. 10865–66). In addition, this data conflicts with ASSA data in the Patel Study. Also, because no statistical analysis was performed, it is impossible to determine

whether the observed differences among brands, in levels of these impurities were due to chance or to the brands.

776. Thus, the comparative data on levels of impurities which respondent acquired after 1974 do not show that Bayer yielded a statistically significantly lower level of ASAN, ASSA, or SSA than other plain 5-grain aspirin brands.

B. *Sterling Did Not Have A Reasonable Basis For Its Claim That BCA Is Therapeutically Superior Or That Such Superiority Has Been Scientifically Established*

777. Dr. Robert John, Medical Director at Glenbrook Laboratories, was unaware of any well-controlled clinical tests addressing the proposition that Bayer Children's Aspirin is therapeutically superior to all other brands of children's aspirin (John, Tr. 5568).

778. Respondent has offered no clinical evidence of the relative therapeutic superiority of Bayer Children's Aspirin.

1. Evidence Other Than Well-Controlled Clinical Studies Fails To Provide A Reasonable Basis For The Therapeutic Superiority Of One Brand Of OTC Plain, Children's Aspirin Over Another

779. The principles discussed in the preceding sections with respect to the need for well-controlled clinical studies for the purpose of substantiating therapeutic superiority claims for Bayer Aspirin generally apply to similar claims for Bayer Children's Aspirin ("BCA").

780. The principles discussed in the preceding sections with respect to the need for well-controlled scientific studies showing statistically significant superiority for the purpose of substituting pharmaceutical superiority claims for Bayer Aspirin [187] generally apply to similar claims for BCA. In the following portions of this section, a number of studies Sterling relies on with respect to BCA will be discussed.

781. Respondent possessed a collection of data consisting of: "Tempurets," by K.R. Klippel, an employee of respondent (March 26, 1968); "TS.20 Tempurets (Children Aspirin) Whitehall Laboratories," by D. Silverhart, an employee of respondent (February 7, 1968); and "TS 29, Bayer Aspirin Children (G–L)," by D. Silverhart (March 21, 1968) (CX 412). This collection's purpose was to present chemical and physical data on Tempurets, a children's aspirin, and to compare *in vitro* dissolution rates of Tempurets, St. Joseph's children's aspirin (St. J.C.) and BCA (CX 412A). The authors reported the following dissolution rates for Tempurets: at 5 minutes, 90% dissolved; at 15 minutes, 101% (CX 412B). The authors went on to plot dissolution rate curves for the three commercial aspirin brands and an experimental BCA formulation (CX 412C, D). One author concluded that Tempurets dissolved faster than BCA and St. J.C. (CXX 412A).

782. The reports in CX 412 do not show that BCA yielded a significantly superior dissolution rate to those of the other two brands. Tempurets dissolved faster that BCA (CX 412A, D). Since the investigators failed to conduct a statistical analysis, it is impossible to determine from this report whether the results are due to chance or to the brands. Since they failed to test more than one lot per brand, no information appears concerning the consistency with which the tested brands might or might not have yielded the plotted dissolution rates. In addition, an investigator explicitly cautioned that the *in vitro* results " . . . should not be interpreted as being related to the actual *in vivo* situation" (CX 412A).

783. Respondent relies on one report of comparative dissolution data which it acquired after 1974 (RX 287). However, this report does not corroborate the proposition that BCA yields a significantly superior dissolution rate to those of all other brands of children's aspirin. In this dissolution test, the investigators measured dissolution rates of 12 brands of children's aspirin: Bowman, Davis, Dewey, Freeda, Oak Park, Pennes, L. Perrigo, St. Joseph, Rexall, Stein-Mendez, Bayer and Sun Laboratories (RX 287Z062–Z070). The authors did not report any findings specifically relating to the children's aspirin (*see* RX 287Z057). Respondent's witness, Dr. Horner, did not conduct a statistical evaluation of the results and it is impossible to determine from this report whether any brand was statistically significantly superior to any other brand.

784. Respondent offered in this proceeding one report of comparative disintegration data, "Analysis and Evaluation off Bayer Children's Aspirin and St. Joseph Children's Aspirin as Found in the United States Homes," by Herbert Terry, of Foster D. Snell, Inc., 1972 (Terry, Tr. 10925–38; RX 184). The purpose [188] of this study was to determine (1) how BCA compared with St. J.C.'s aspirin, found in households, in terms of certain pharmaceutical parameters, and (2) whether these products revealed differences in manufacturing uniformity (RX 184E). After the samples were collected from households, employees of Snell conducted various tests, including disintegration. This record indicates that this test's methodology had certain deficiencies. F. 644, *supra.*

785. The investigators in RX 184 reached the following conclusions concerning one disintegration test (RX 184Z003): (1) no statistically significant difference existed between the two brands' average rates for beginning and for completing disintegration; (2) BCA registered no failures of the test while St. J.C. registered a 5% failure rate (RX 184Z003). Concerning a second disintegration test (RX 184Z004), the investigators reported: (1) no statistically significant difference existed between the two brands for average rates of complete disintegra-

tion; and (2) neither brands' samples failed the test (RX 184Z004). In addition, the author's application of utility ratings resulted in the two brands receiving equal or closely comparable ratings in the first disintegration test (RX 183Z003–04). The author did not apply utility ratings to the results generated by the second test (RX 183Z004).

786. The comparative disintegration data which respondent had presents an inconclusive picture about BCA's disintegration rate in comparison with that for one other brand of children's aspirin.

787. The recommended children's dosage of aspirin for the relief of mild to moderate pain varies with age, from two tablets, 162.5 mg, for children of two to under four years old, to 6 tablets, or 487.5 mg, for children of 11 to under 12 years old (CX 466, pp. 35489–90). To measure the aspirin content of tablets, aspirin assays are conducted in laboratory analyses (Miller, Tr. 6733, Rhodes, Tr. 11643).

788. Respondent offered three reports of comparative children's aspirin content data, including a collection of data appearing in: "PD.56–T Bayer Children's Aspirin, Improved Flavor," by Dr. J.E. Wolff, an employee of respondent (April 19, 1961); "PD.56–T Bayer Children's Aspirin, Improved Flavor," by Dr. J.E. Wolff (May 19, 1961); and "Bayer versus St. Joseph Aspirin for Children," by Dr. J.E. Wolff (February 23, 1962) (RX 161). In this series, the authors report physical and chemical data, including aspirin content data, on two dozen bottles each of BCA and St. J.C. (RX 161A). For each brand, eight bottles were stored under three different storage conditions (RX 161A). The author reported the following results from an initial test and from a test after 12 months storage at 37°C/50% relative humidity, respectively: BCA - 83.1 mg and 80.2 mg; and St. J.C. - 80.2 mg and 79.5 mg (RX 161C). It is impossible to [189] determine from this report whether the differences for BCA and St. J.C. reflected differences in age of the tablet, conditions of storage prior to purchase, chance, or the brands. Also, it is impossible to draw conclusions from this data about the brands' dosage uniformity (Banker, Tr. 12967).

789. Respondent also offered "Analysis and Evaluation of Bayer Children's Aspirin and St. Joseph's Children's Aspirin as Found in United States Homes" (RX 184). The investigators failed to control for age of the tablets and conditions of use or storage. The author reported that the two brands registered as equivalent in aspirin content and that neither registered failures according to two different test limits (RX 184Z002) and that, according to his application of utility ratings, both brands received the same rating (RX 84Z002). The report clearly shows that no statistically significant difference existed between the brands' averages for aspirin content (RX 184Z002).

790. Respondent offered one report of comparative children's aspirin content data which it acquired in 1974 (RX 287). However, this

report does not corroborate the proposition that Bayer Children's Aspirin yields a significantly superior amount of aspirin per tablet or more consistently yields 100% of label claim than all other brands of plain children's aspirin. In this test, the investigators measured the aspirin content of 13 brands of children's aspirin, *i.e.* Bowman, Davis, Dewey, Freeda, Oak Park, Pennes, L. Perrigo, St. Joseph, Rexall, Sein-Mendez, Bayer Children's Aspirin, Sun Laboratories, and Westward (RX 287V–Z009). The authors did not report any findings specifically relating to the children's aspirin (*see* RX 287K). Respondent's witness, Dr. Horner, did not conduct a statistical evaluation of the results and it is impossible to determine from this report whether any brand was statistically significantly superior to any other brand. It is also impossible to determine the extent to which the results are due to the samples' age or conditions of storage.

791. Respondent offered comparative FSA data appearing in RX 161, wherein the authors reported the following results from an initial test and from a test after 12 months' storage at 37°C/50% relative humidity, respectively: BCA - 0.2% and an illegible figure; and St. J.C. - 0.3% and 0.14% (RX 161A, C). The investigators reported FSA levels in another measure, *i.e.,* HA/FA (Banker, Tr. 12964–65; 12761–67): BCA - 0.07% and 0.07%; and St. J.C. - 0.11% and 0.52% (RX 161A, C). It is impossible to determine from this report whether the differences for BCA and St. J.C. reflected differences in age, conditions of storage prior to purchase, chance, or the brands.

792. Respondent also offered "Analysis and Evaluation of Bayer Children's Aspirin and St. Joseph's Children's Aspirin as Found in United States Homes" (RX 184). The investigator reported that St. J.C. yielded four times as much FSA than BCA **[190]** (RX 184Z004). According to one test limit, BCA registered no sample failures while St J.C. registered a 9% failure rate (RX 184Z005). According to another test limit, BCA registered a 22% failure rate and STC registered a 100% failure rate (RX 184Z005). Applying utility ratings, the author attributed a rating of "7" to STC registered a 100% failure rate (RX 184Z005). Applying utility ratings, the author attributed a rating of "7" to BCA and "0" to St. J.C. (RX 184Z005). Upon cross-examination, the author stated that if the assumptions underlying his application of utility ratings changed, the ratings would also change (Terry, Tr. 11015). Specifically, the utility ratings could change from 7.0 to 9.0 for BCA and from 0.0 to 6.0 for St. J.C. (Terry, Tr. 11018-19). The author testified that it would be "inconsistent with the total data" to attribute high utility ratings to products for which some samples failed official standards (Terry, Tr. 11026–28). It would also be "inconsistent with the total data" to attribute a utility rating of 0.0 to a a product whose samples manifested a 91% passing rate according to the official

standard, *i.e.*, "0" to St. J.C. where 91% met the official FSA standard (RX 184Z005).

793. Respondent offered one report of comparative FSA level data which it acquired after 1974 (RX 287). However, this report does not corroborate the proposition that BCA yields a significantly lower FSA level than all other brands of OTC plain, children's aspirin. In "National Survey I" the investigators measured FSA levels of 13 children's aspirin brands. In "National Survey II" the investigators measured FSA levels of seven children's aspirin brands (RX 287Z025–Z026). Since this test did not include Bayer Children's Aspirin, it does not offer FSA data on BCA in comparison with other brands of children's aspirin. At any rate, it is impossible to determine from this report whether any brand was statistically significantly superior to any other brand.

794. Respondent offered one report of comparative data concerning levels of impurities which it acquired after 1974 (RX 287). However, this report does not corroborate the proposition that BCA yields a significantly lower level of ASAN, ASSA, or SSA than all other brands of OTC plain, children's aspirin. In this test, the investigators measured levels of these impurities for 13 brands of children's aspirin, *i.e.*, Bowman, Davis, Dewey, Freeda, Oak Park, Pennes, L. Perrigo, St. Joseph's, Rexall, Sein-Mendez, Bayer, Sun Laboratories, and Westward (RX 287Z035–Z046). The investigators did not report any findings specifically related to children's aspirin. No statistical evaluation of the test results was conducted.

795. The record indicates that during 1969–1974 at least two other brands of plain children's aspirin were available for purchase, *i.e.*, Tempurets and St. Joseph's Children's Aspirin. It further indicates that more recently, *e.g.*, since 1976, numerous brands of children's aspirin were available for purchase (Banker, Tr. 12635–37; RX 287Z062–Z070). **[191]**

796. For all of the reasons discussed hereinabove, at the time of the representation alleged in the Complaint, Paragraph 10(b), no reasonable basis existed for the representation that BCA is superior in terms of significant therapeutic effect to any other children's aspirin, because respondent lacked competent and reliable scientific evidence sufficient to support this representation. For the same reason, no reasonable basis existed for the representation that BCA is pharmaceutically superior to any other children's aspirin, because respondent lacked well-controlled scientific study which showed statistically significant superiority for BCA in terms of pharmaceutical characteristics.

797. Therefore, respondent's implied claim that it has been estab-

lished that Bayer Children's Aspirin is therapeutically superior to any other children's aspirin is false.

798. Because Bayer Children's Aspirin's therapeutic superiority has not been established according to the criteria set forth and adhered to by qualified experts in the scientific community, was made in the face of a substantial question recognized by such experts as to its validity, as alleged in Complaint Paragraph 9.

C. *Sterling Did Not Have A Reasonable Basis For Its Claim That Cope Is Therapeutically Superior Or That Such Superiority Has Been Scientifically Established*

1. The Ingredients in Cope

799. The formulation of Cope includes 421 mg of aspirin, 32 mg of caffeine, 50 mg magnesium hydroxide, 25 mg aluminum hydroxide gel and 12.5 mg methapyrilene fumarate (Moertel, Tr. 6340).

800. The nature and quantity of ingredients in a drug is not evidence that can establish its therapeutic superiority to other drugs. Thus, the fact that two tablets of Cope contain more analgesic compared to plain aspirin (which contains 650 mg of aspirin or Anacin which contains 800 mg aspirin), as well as four other ingredients, is insufficient to establish that it produces more effective relief.

Amount of Aspirin

801. Respondent relied upon a number of studies which measured clinical responses to graded doses of aspirin to show that the dose response relationship is such that it may be inferred that more analgesic (*i.e.,* 842 mg in Cope as compared to 650 mg standard dose) necessarily provides more analgesia. However, Dr. George Goldstein, Medical Director of Glenbrook [**192**] Laboratories, agreed that the dose response curve for aspirin between the levels of 600 mg to 1500 mg is relatively flat (Goldstein, Tr. 15614), and that increments between these two dosages would not tend to provide greater relief than 650 mg of aspirin. Dr. Goldstein agreed that Sterling's competitors have tried unsuccessfully for years to establish that doses larger than the standard 650 mg dose of aspirin produce greater pain relief (Goldstein, Tr. 15614; CX 466, p. 35364).

802. The Fiscal Report of FDA's OTC Internal Analgesics Panel confirms the absence of a proven association between more milligrams of aspirin and greater pain relief:

> . . . [T]here are no data available to show that multiple dosages greater than 650 mg will provide any greater clinical benefit for analgesic and antipyretic effects. (CX 466, p. 35364)

803. Of the evidence relied upon by respondents to support the proposition that increased dosages of aspirin provides increased analgesia, none of the studies compared the increased amount of analgesic in Cope to 650 mg of aspirin. For example, respondent relied upon a study by Murray (RX 250-Murray) wherein he tested graded doses of aspirin up to 650 mg for effectiveness in treatment of common headache. The author concluded that the only effective dose of aspirin was 650 mg. The study provided no data on the relative efficacy of doses greater than 650 milligrams (RX 250-Murray Table II). Respondent also relied on an abstract of a study by Dr. Sunshine measuring the dose response of aspirin in post-partum patients with either episiotomy or uterine cramping pain. Dr. Sunshine measured the dose response for aspirin at 150 mg, 300 mg, 400 mg, 600 mg, 1200 mg and 1800 mg. The study draws no conclusions as to any difference which may exist between 842 mg of aspirin and a 650 mg dose (RX 250-Sunshine, 1968). In fact, the abstract offered in evidence only states "significant differences at the 5% level or better were noted between several doses of aspirin, favoring the higher doses," without providing more specific data (RX 250-Sunshine, 1968). Finally, respondent cited a study by Dr. Parkhouse which compared dosages of 300 mg, 600 mg and 1200 mg of aspirin in five studies measuring relief of post-operative pain. Two of the studies showed no greater pain relief obtained from 1200 mg than from 600 mg. At no time was a statistically significant difference in pain relief shown in a direct comparison between 600 mg and 1200 mg (RX 250-Parkhouse; Goldstein, Tr. 15614). The Parkhouse study also made no direct comparison between the standard dose of aspirin, 650 mg, and the amount in Cope, 842 mg (Goldstein, Tr. 15614).

804. Dr. Monroe Trout, Sterling's Vice President, in comments submitted on behalf of Sterling Drug to the FDA OTC Analgesics Panel stated in 1974 that: **[193]**

> . . . it should be noted in regard to pain relief, that the general scientific consensus is that existing combinations of aspirin with other OTC ingredients *and aspirin at higher dose* levels, are not superior to 650 milligrams of straight aspirin" (CX 456M).

Caffeine as an Analgesic or Adjuvant

805. Caffeine is not an analgesic. The FDA Analgesics Panel concluded that caffeine alone was an ineffective pain reliever, and it placed caffeine in Category II as an analgesic (CX 466, p. 35482). Moreover, the effect of caffeine as an adjuvant to aspirin or acetaminophen has not been established (Moertel, Tr. 6312–15), and the FDA OTC Analgesics Panel classified the adjuvancy effect of

caffeine in Category III (insufficient information to determine the safety and effectiveness) (CX 466, p. 35482).

806. Two editions of the *AMA Drug Evaluations* (CX 467 and CX 468), a reliable and well-recognized text on drug therapy, found no evidence that caffeine in the amounts present in combination products with the same amount of caffeine as Cope has any potentiating effect on analgesic activity (CX 467I; CX 468G).

807. The *Medical Letter* (CX 460), admitted as collaborative evidence supporting complaint counsel's case, and a reliable and well-recognized publication, reviewed evidence concerning the addition of caffeine to aspirin, and found that it had not been established that difference in analgesia was attained through the addition of caffeine to analgesics.

808. There is no evidence in this record in the form of well-controlled clinical tests in humans which demonstrates that caffeine contributes to analgesic effect when it is combined with aspirin (Moertel, Tr. 6314, 6316). Respondent relied on studies in animals by Vinegar which indicated an analgesic adjuvancy effect for caffeine (Goldstein, Tr. 15637). However, animal studies are unreliable predictors of analgesic efficacy in man, and are therefore unacceptable for establishing the analgesic effect of caffeine (Fields, Tr. 16729).

809. Respondent also relied upon studies by Dr. Lim in which experimental pain was induced in man (Goldstein, Tr. 15637). It was observed that the addition of caffeine to the combination of aspirin and acetaminophen produced more pain relief from pain induced by bradykinin intraperitoneally. The FDA's Panel on OTC Internal Analgesics which reviewed the Lim Study noted that its authors concluded that more work needed to be done on the potentiating effect of caffeine (CX 466, p. 35484). Moreover, the OTC Analgesics Panel reviewed other experimental pain studies and concluded: **[194]**

> Analgesic tests and most methods employing experimental pain in normal human volunteers have failed to predict with any consistency the clinical performance of analgesic drugs particularly those used for OTC medication (CX 466, p. 35444).

Respondent's expert Dr. Fields agreed with the Panel's assessment (Fields, Tr. 16728–29).

810. Respondent also relied on a study by Wojcicki *et al.*, performed in Poland, and translated into English, as support for its position on caffeine. This was, in part, an outpatient study, and one of the two groups under study suffered from common headache (Goldstein, Tr. 15658; Fields, Tr. 16734–35). Failure to do so suggests that whatever results were reported may have been due to chance. The results reported by the authors are categorized by terminology different from

that used by the subject in responding to questions about their pain (Fields, Tr. 16734). Subjects were asked to fill in the results of treatment as "pain disappeared," "pain markedly reduced," "pain unchanged" or "pain worse." The authors reported results as "no more pain," "pain greatly improved," "pain slightly improved" and "pain unchanged" (Fields, Tr. 16734; Goldstein, Tr. 15658). Although one may speculate about potential errors in translation of the terms in the Polish manuscript, Drs. Goldstein and Fields agreed that the results were reported in language different from the questionnaire and that the reader cannot tell whether the definitions or terms were changed (Fields, Tr. 16734). For this reason the Wojcicki study is confusing and it cannot be considered a well-controlled study.

811. Respondent also relied on a study by Houde and Wallenstein in which they compared aspirin to a combination of aspirin, phenacetin and caffeine (RX 197). The study did not test an aspirin-caffeine combination against caffeine (RX 197). The authors concluded that "the results with caffeine must be considered equivocal, although it is possible that dosage may be an important factor, and caffeine may simply be ineffective at much below the 60 mg dose" (Fields, Tr. 16736; Goldstein, Tr. 15644). In fact, this study was presented to the FDA Panel on OTC Internal Analgesics which concluded that it was the only "well-controlled clinical study to determine whether aspirin plus caffeine is more effective than aspirin alone, and the results of this study are equivocal" (CX 466, p. 35483). Even though the FDA Panel considered this study, the study's equivocal results and the absence of other sound evidence led the Panel to place caffeine in Category III as an adjuvant.

812. CX 461, a study by Dr. Moertel, entitled "Relief of Pain by Oral Medication—A Controlled Evaluation of Analgesic [**195**] Combinations," published in *The Journal of the American Medical Association,* volume 229 (1974), is the only clinical study in evidence which has directly compared aspirin with and without caffeine. The study was designed as a randomized, double-blind cross-over study comparing analgesic combinations in relief of cancer pain. The combination of aspirin and caffeine was not shown to afford greater pain relief than aspirin alone. In fact the combination performed more poorly than aspirin although not at a statistically significant level (Moertel, Tr. 6316–21).

813. Dr. Moertel testified that, subsequent to publication of his study (CX 461), he was contacted by respondents who asked if they might review it for possible use in a New Drug Application. After the study was reviewed by respondent's statisticians, Dr. Moertel was commended for his work and it was agreed that respondent might rely

on the study as support for its New Drug Application (Moertel, Tr. 6581).

814. Neither of respondent's experts who testified on the effect of caffeine, Dr. George Goldstin and Dr. William Fields, was familiar with or had considered Dr. Moertel's study in reaching conclusions about the analgesic or adjuvant effect of caffeine in combination with aspirin (Goldstein, Tr. 15641; Fields, Tr. 16737).

815. None of the three studies offered by respondent, and discussed hereinabove, either alone or in combination, supports the proposition that caffeine acts as an adjuvant in combination with aspirin. The studies employed unreliable experimental pain models, produced ambiguous results lacking statistical analysis, which were reported in a manner inconsistent with the way the data was generated, or, when well controlled, produced equivocal results. Moreover, the only clinical study which directly compared plain aspirin to aspirin and caffeine concluded that the aspirin and caffeine combination afforded no greater pain relief than aspirin alone (CX 461; Moertel, Tr. 6316–21). Therefore, the record as a whole demonstrates that the effect of caffeine as a potentiator or adjuvant to aspirin has not been established (Moertel, Tr. 6322; CX 466, pp. 35482–84).

Caffeine as a Vasoconstrictor

816. Caffeine is a member of a class of chemicals known as xanthines (RX 250, Dispenstory, p. 220). Caffeine has been described as a central nervous system stimulant that acts on the kidneys to produce a mild diuretic effect, and on the vascular system to cause a constriction of blood vessels in certain parts of the body, stimulating cardiac response and relaxing smooth muscles (CX 466, p. 35483). Caffeine acts on the scalp and internal skull within the brain, causing initial constriction of blood vessels at first and eventual dilation of them, thereby enlarging the diameter of the blood vessels so that blood can flow more easily. This mechanism acts to reduce headache pain [**196**] (Fields, Tr. 16632; CX 466, p. 35483). Respondent presented evidence that caffeine may act as a vasoconstrictor and thus should help to relieve certain types of headache pain resulting from dilation of cranial blood vessels.

817. The FDA's Panel on OTC Internal Analgesics considered the etiology of headaches and concluded that headaches have been separated into three major groups: vascular, psychogenic and traction-inflammatory headaches (CX 466, p. 35352). A common feature of all vascular headaches is physiological change in the cranial blood vessels. In a majority of cases there is a tendency for vasocilation which provokes the headache (CX 466, p. 35352). There are two types of vascular headaches—hypertensive (which is related to elevation in

blood pressure) and migraine (a throbbing, unilateral head pain). The OTC Analgesics Panel concluded that "OTC analgesics are usually not appropriate for the treatment of hypertensive or migraine headaches which require diagnosis of the disease by a physician and usually treatment with drugs available only by prescription (CX 466, p. 35353).

818. Nervous tension headaches (or psychogenic headaches) comprise the majority of headaches (Goldstein, Tr. 15670) and are to be distinguished from vascular headaches. They usually are associated with muscle contraction (CX 466, p. 35353). According to the final report of the OTC Panel on Internal Analgesics:

these headaches are not vascular in nature or associated with traction or inflammation. Psychogenic headaches, which may account for up to 90% of the chronic headaches seen by the physician [may be caused by] . . . the individual's marital relations, occupation, social relationships, life stresses, and habits (CX 466, p. 35353).

819. Caffeine has a vasoconstrictor effect in the head and may therefore be helpful in relieving vascular headache pain caused by vasodilation of cranial blood vessels (Fields, Tr. 16631; Goldstein, Tr. 16666). However, caffeine's vasoconstrictor effect has not been thought to provide any benefit to the other more common psychogenic headache. Articles relied upon by respondent to support the rationale of combination products indicate that tension headaches (or psychogenic headaches) account for the majority of headaches (RX 250-Lederer, p. 26; *see,* F. 818, *supra*), while vascular headaches occur in a small percentage of the population ranging from 4%–15% (RX 250-Caviness).

820. The limited utility of caffeine as a vasoconstrictor is supported by an article in which Dr. Harold G. Wolff, a recognized headache expert (Fields, Tr. 16719) opposed the idea [**197**] of using aspirin in combination with caffeine because caffeine is helpful in relieving only a small percentage of headaches. Respondent has relied upon this article (Fields, Tr. 16635–36). Dr. Wolff stated that where necessary and appropriate, pysicians should prescribe caffeine separately (Goldstein, Tr. 15667; Fields, Tr. 16719; RX 250-Gold, p. 149). Dr. Wolff also stated that:

no patient with vascular headache whether the pure migraine type or not, should be turned loose with an analgesic or a vasoconstrictor. Every patient should have explained to him the dynamics of the attack . . . (RX 250-Gold).

821. Respondent presented no persuasive evidence which shows that caffeine at the 65 mg dose found in Cope will benefit individuals with vascular headaches (Goldstein, Tr. 15678). In fact, respondent's

expert witness, Dr. Fields, a neurologist, agreed that it is not known at what dose caffeine begins to exert its vasoconstrictive effect. He speculated that it is probably not effective in amounts less than 60 mg (Fields, Tr. 10726). In drawing conclusions as to its usefulness in treating the relatively infrequent vascular headache, Dr. Fields relied predominantly on his experience and articles which referred to the beneficial effect in some vascular headache victims of the caffeine generally found in a cup of coffee. But the average amount of caffeine in a cup of coffee, based on the literature relied upon by respondent, is about 100 mg, *i.e.*, 30% greater than that found in a 2–tablet dose of Cope (RX 250-Berland; RX 250-Krantz; RX 250-Dispensatory).

822. The record as a whole is inconclusive about the dose at which caffeine acts as a vasoconstrictor in cranial blood vessels. Moreover, the number of individuals who suffer from vascular headaches for which caffeine *may* be beneficial is small, and those individuals should be under a physician's care rather than relying on self-medication.

823. There is also some evidence that caffeine may aggravate pain rather than relieve it. Dr. Tainter of Sterling, in a memo to G.W. Johnson written on May 20, 1971, stated his belief that:

> the evidence on caffeine is not conclusive, but it suggests that caffeine by its power to heighten the sensitivity of the entire central nervous system may in fact make pain more intense and that this tends to diminish the analgesic effectiveness of compounds which would tend to make pain less intense. (CX 417B). [198]

824. And, in a draft of its "Blue Book" (CX 413), respondent quoted Dr. William Beaver, a recognized authority in the field of analgesic research (Goldstein, Tr. 15650) stating:

> Considering an aspirin-caffeine formulation, a leading scientist has observed recently before the same congressional subcommittee that the combination could no longer be justified on the basis of any therapeutic rationale that I'm aware, and further, if anything, the caffeine component would increase the incidence of stomach upset. (CX 413K).

Buffers in Cope

825. Cope contains two buffers: 50 mg magnesium hydroxide and 25 mg aluminum hydroxide gel.

826. Respondent's representation that Cope is a more effective pain reliever for nervous tension headache than any other analgesic (Complaint ¶ 9A 3) is premised in part upon the theory that buffers, in combination with analgesics, speed dissolution (Goldstein, Tr. 15678). This increased rate of dissolution is claimed to result in higher, more

rapid blood levels of the analgesic presumably making it a more effective, and faster pain reliever.

827. The consensus of experts who testified in this proceeding is that blood level data cannot be used to establish the superior clinical effectiveness of an analgesic agent (Moertel, Tr. 6291; Grossman, Tr. 7577; DeKornfeld, Tr. 8408–11; Feinstein, Tr. 16479; Danhof, Tr. 17269), because blood levels have not been correlated with either the degree, onset or duration of analgesia (F. 469, 502, *supra*). Furthermore, the record contains no evidence of any blood level studies comparing Cope to any other OTC analgesic product.

828. Dr. George Goldstein stated that it is Sterling's position that buffered analgesics are not in fact superior to unbuffered aspirin in therapeutic performance (Goldstein, Tr. 15686). In remarks to the FDA OTC Analgesics Panel in 1976, Dr. Goldstein said that as far as claims for buffered aspirin are concerned, he disagreed with the Panel's conclusion to place these claims in Category III (that there is insufficient data to permit final classification of the claims). He stated further that, with respect to increased rate of absorption, decreased incidence of gastric distress or the inference of greater safety, there had been an "unusually large number of unsuccessful attempts to prove such claims . . . . for two decades." (CX 574C). He reminded that Panel of a statement that "getting into the bloodstream faster is only important if one has painful blood . . ." (CX 574D). **[199]**

829. Respondent's witness, Dr. Monroe Trout, Vice President and Director of Medical Affairs, stated that it was Sterling Drug's position between 1970 and 1975 that the addition of buffers to a analgesic tablet did not result in a tablet that provided faster relief (Trout, Tr. 16136–44).

2. Clinical Studies in Humans on the Efficacy of Cope

830. The only clinical studies which bear on the comparative effectiveness of Cope are those studies which compare Cope itself to other analgesics in patients suffering headache pain. Respondent's reliance on studies by Dr. Arnold Friedman in which he tested Fiorinol, an analgesic-barbiturate combination, do not provide adequate substantiation for Cope's claims of superior efficacy for relief of nervous tension headache pain. Cope, unlike Fiorinol, contains no barbiturate and Dr. Friedman did not test relief of nervous tension headache pain.

831. Food and Drug Research Laboratories ("FDRL") is a commercial laboratory which conducts safety and efficacy studies for drug companies and government agencies on a contractual basis (Carson, Tr. 15828–31). Dr. Steven Carson, a former FDRL vice-president, described FDRL's expertise as in toxicology or safety studies (Carson, Tr. 15979). Dr. Carson, himself a pharmacologist and toxicologist, was the

only witness called by Sterling to testify regarding the FDRL studies performed for Sterling.

832. Dr. Carson was contacted by Dr. Tainter for Sterling and asked to set up clinical studies for Cope (to be known as Tenquel in the studies) and Vanquish (Carson, Tr. 15850). Dr. John Silson, whom Dr. Tainter knew and regarded as a suitable investigator for the studies, was retained by FDRL as a consultant (Carson, Tr. 15833) from 1962 through 1969 and subsequently became a vice-president of the company for two years. Dr. Silson was responsible for drawing up the protocols for these studies (Carson, Tr. 16000–01) and carried out, monitored, controlled and evaluated the studies (Carson, Tr. 15851). Dr. Carson reviewed the protocols and was responsible for subsequent contacts with the client concerning organization and administration of the clinicals (Carson, Tr. 15997–16000). For example, it was his duty to get the properly labeled drugs to the clinicians as well as to answer any questions from the clinicians (Carson, Tr. 15899). In the course of contacts with the client, Dr. Carson said that there were occasional breakouts of data or "interim reports" (Carson, Tr. 16000). Drafts of reports were drawn up by Dr. Silson and submitted to Dr. Carson for routine review (Carson, Tr. 15851).

833. Four clinicals on Cope (Tenquel) were submitted by FDRL to Sterling Drug: [200]

(1) RX 237, "Protocol-Evaluation of an Analgesic-Sedative Preparation" dated 1964, includes correspondence between Sterling and FDRL as well as in Interim Summary Report - Clinical Investigation of Tenquel in Human Volunteers, June 12, 1964, signed by Steven Carson, Pharmacologist, and "II Use Test," dated August 18, 1964, and signed by Steven Carson, Pharmacologist;

(2) RX 236, Report - Clinical Evaluation of Tenquel, September 7, 1965, signed by John E. Silson, Clinical Consultant and Steven Carson, Pharmacologist;

(3) RX 238 "Report - Double-Blind Cross-Over Evaluation of Tenquel Compared with Regular Aspirin in Tension Headache, May 5, 1969, signed by John Silson, Clinical Consultant and Steven Carson, Ph.D., Director, Biological Divisions; and

(4) RX 239, "Report - Double-Blind Cross-Over Comparison of Cope with Anacin in Relieving Tension Headaches, July 21, 1971, signed by John Silson, M.D., M.P.H., Research Consultant, and Steven Carson, Ph.D., Scientific Director.

834. Of the four clinical tests performed on various formulations of Cope, two were double-blind cross-over studies which compared Cope with plain aspirin (RX 238) and with Anacin (RX 239). Neither of the two included a placebo control. The other clinicals (RX 236 and 237)

compared two different formulations of Cope with placebo but did not involve any comparison with aspirin or any other OTC analgesic product.

835. The FDRL Cope studies were designed to employ several clinical investigators (Carson, Tr. 15851). Among the facilities used in the studies and provided the clinical investigators was the laboratory of LaWall and Harrison in Philadelphia, a firm no longer in business because of lack of financial support (Carson, Tr. 15852, 16056). FDRL also used the services of Dr. Morris Schelansky who became director of FDRL's industrial biology division in Philadelphia. Dr. Schelansky in turn recruited local physicians to run the studies according to the protocols developed by Dr. Silson (Carson, Tr. 15854). Test drugs were provided to the investigators by Dr. Carson and FDRL received back the completed questionnaires for statistical analysis (Carson, Tr. 15854). **[201]**

836. The record includes an abbreviated version of protocol for one of the studies (RX 237). It does not contain any reference to a statistical methodology to be employed in the study. In fact, no such data is provided in any of the FDRL studies. And in one study (RX 238) the statistical methodology was changed in midstream after the investigators learned that the study as originally designed was not going to show any difference between the two drugs (Moertel, Tr. 6346, 6274; DeKornfeld, Tr. 8431). This smacks of statistical manipulation and is not acceptable scientific methodology (Moertel, Tr. 6346).

837. According to Dr. Carson, the patient population for CX 237 consisted solely of women (Carson, Tr. 15888). They were drawn from women visiting the offices of pediatricians who complained about tension problems associated with child rearing (Carson, Tr. 15888). They were evaluated for headache, nervous tension, depression and generalized aches and pains (Carson, Tr. 15888). The last two criteria (depression and generalized aches and pains) were dropped from RX 238 and 239 (Carson, Tr. 15926). The patient population in the three other studies included both sexes (Carson, Tr. 15916, 15945).

838. The subjects chosen to participate in the study on an outpatient basis were given initial questionnaires to fill out in order to determine the frequency of their headaches (RX 237; Carson, Tr. 15893). Although Dr. Carson testified that frequent headaches were a requirement for participation in the study (Carson, Tr. 15893), neither the protocol (RX 237C, D) nor the Patient Selection Questionnaire (RX 237K) reflects that requirement. In fact, qualifying symptoms were not limited to headaches. The protocol says, "Patients will be evaluated for pain, headache, emotional tension, spasm, general malaise and mood . . ." (RX 237C) and the questionnaire notes that individuals should be rejected ". . . if none of the symptoms shown in a, b, c, or

d [headache, nervous tension, depression or general aches and pains] occur less frequently than once weekly (RX 237).

839. Although Dr. Carson testified that everyone selected in any of the studies was required to have a headache, he agreed on cross-examination that only 731 of the 894 participants in RX 236 reported having headache (Carson, Tr. 16041–45; RX 2360). Thus it would appear that 163 participants, or almost 20% of the entire patient population, were given medication and reported results relating to a condition from which they did not suffer.

840. The formulation tested in RX 237 was different from that tested in the other clinicals (RX 236, 238 and 239). The RX 237 Cope formulation included 194 mg aspirin, 128 mg acetophenetidin, 12.5 mg methapyrilene fumarate, 32 mg caffeine and buffers (Carson, Tr. 15902). The formulation tested in RX 236 increased the amount of aspirin to 421 mg and eliminated acetophenetidin (Carson, Tr. 15902). The formulation tested in **[202]** RX 238 and 239 also did not include acetophenetidin (Carson, Tr. 15930), and the amount of caffeine included in the RX 239 formula was 30 mg as compared to 32 mg in the other formulations. Dr. Carson did not know how the above formulations compared with the marketed version of Cope (Carson, Tr. 16062).

841. In RX 236 and 237, the patients were given eight tablets of medication. If no relief was obtained from two tablets in the first hour, they could immediately take the second two tablets (Carson, Tr. 15894). Thereafter they could take the remaining medication at four-hour intervals (Carson, Tr. 15894). In RX 238 and 239, subjects were given only enough medication for a first dose and could take whatever their usual medication was—whether OTC or prescription—as a second dose after one hour (Carson, Tr. 15894; RX 238B).

842. Two questionnaires were given to the subjects who participated in RX 236 and 237. Each form was to be filled out at home by the subjects after taking each medication (Carson, Tr. 15934). The questionnaires used in RX 238 and 239 were not included in those reports but, according to Dr. Carson, they were modeled after the one accompanying RX 237 (Carson, Tr. 16028–35). The instructions printed on the back of the form told the subjects to record the severity of the symptoms experienced—whether severe, moderate, slight or none—and the degree of relief for each symptom obtained from each medication—complete, marked, slight, none, worse or none initially (RX 237G, H). Both RX 236 and 237 accepted subjects who complained of headache, nervous tension, depression and generalized aches and pains. Depression and generalized aches and pains were dropped from RX 238 and 239.

843. Dr. Carson testified that the questionnaire in RX 238 and 239 asked each subject who presumably had a headache when selected to

distinguish a "nervous tension headache" from an ordinary headache, without the aid of any definitions or instructions (Carson, Tr. 16036). In effect, a subject was asked to self-diagnose his or her condition (Carson, Tr. 16036). At no time were any of the subjects' self-diagnoses subject to clinical confirmation (Carson, Tr. 16036–38). Because both RX 238 and 239 specifically sought to determine whether Cope was more effective than aspirin or Anacin for the relief of nervous tension headache, Dr. Carson agreed that if a subject was actually suffering from a simple headache and wrongly self-diagnosed the headache as a nervous tension headache, the study results would be misleading (Carson, Tr. 16036–38). RX 250, Ad Hoc Committee on Classification of Headaches, defines fifteen major headache classifications. These classifications were to be used by physicians for diagnostic purposes.

844. The subjects were to report back results to the clinical investigators after a two-week period. Thus, the **[203]** results were dependent not only on the subject's accurate self-diagnosis, but also upon his prompt and accurate recordation of the answers or his flawless memory. Participants reported having at least one headache a week and frequently more (RX 238, p. 6). Therefore, if a subject with two or three headaches per week did not fill out a questionnaire promptly, it is likely that the data might reflect results of other medication taken to relieve subsequent headaches. It would have been even harder during the second week to compare the relief from that week's medication with the previous week's when the subject suffered multiple headaches within a single week. Dr. Carson did not testify to any controls built into these studies to assure prompt and accurate data recordation. Given the problems described above with respect to RX 237, it is just as likely that similar problems existed in RX 238 and 239. These out-patient studies thus failed to assure accurate and prompt data collection (Moertel, Tr. 6468–69).

845. None of the four FDRL studies on various formulations of Cope was published or subjected to peer review (Carson, Tr. 15973) and none was replicated by an independent investigator (DeKornfeld, Tr. 8434).

846. A number of ambiguities remain unresolved which cast a shadow upon the reliability of RX 238. First, it is not clear what the true amount of methapyrilene fumarate was in the tested formulation. The report submitted to Glenbrook Labs contains a handwritten notation in the text of the "Basic Design" section changing "12.5 of methapyrilene fumarate" to what appears to be "7" (RX 238B). Dr. Carson testified that he did not know who was responsible for this alteration (Carson, Tr. 15930). If the text was intended to read "7.5 mg methapyrilene fumarate," then Dr. Carson pointed that it referred to 7.5 mg of methapyrilene *base* which, he says, is equal to 12.5 mg of

methapyrilene *fumarate* (Carson, Tr. 16026–28). However, the altered text reads 7 mg of "methapyrilene fumarate" (RX 238B). Dr. Carson's explanation would not be applicable if the numbers were in fact meant to read "7" mg as opposed to "7.5" mg.

847. Second, the report (RX 238) did not include questionnaires and none are available now (Carson, Tr. 16028–35). Dr. Carson testified that the four Cope clinicals should be looked at as a single package (Carson, Tr. 15928–29). Dr. Carson assumed that the questionnaires from either RX 236 or RX 237 was used for RX 238. However, on cross-examination he agreed these questionnaires included measurements and questions relating to symptoms which were not included in RX 238—specifically "depression" and "general aches and pains" (Carson, Tr. 16030). According to Dr. Carson, these symptoms were dropped from the questionnaire subsequently used in RX 238 because so few people had responded that they suffered those symptoms (Carson, Tr. 15926). **[204]**

848. The results of the two comparative studies, RX 238 and 239, are insufficient to support a conclusion that Cope is more effective than plain aspirin or Anacin for relief of nervous tension headaches. In RX 238, the results do not show a statistically significant different in pain relief scores between Cope (Tenquel) and aspirin (Moertel, Tr. 6347). RX 239 (comparing Cope with Anacin) shows no statisticaly significant difference between the two drugs in complete relief (RX 239, Table 4; Moertel, Tr. 6349), and no statistically significant difference between the two drugs in the relief index (Moertel, Tr. 6349; RX 239, Table 6).

849. Dr. Carson testified that the FDRL studies on Cope were to be looked at as a series, parts of a "factorial design" (Carson, Tr. 16045–51). He defined such a design as one which has in mind a single protocol or a protocol where most of the materials are common to all (Carson Tr. 16050). However, he could not say that this factorial design was in fact agreed to and authorized in advance by Dr. Tainter on behalf of Sterling (Carson, Tr. 16050–52). He merely testified that in 1963 in correspondence with Dr. Tainter, the "concept of subsequent studies was raised" (Carson, Tr. 16051). That concept was raised to account for the fact that two of the trials did not include a placebo control. A comparative analgesic trial should include a placebo *and* aspirin as a standard "since if no measurable superiority to aspirin can be demonstrated the product is not likely to be of interest" (RX 237C; Carson, Tr. 16052). The earliest trials on Cope, RX 236 and 237, did not include a comparison to aspirin whereas the later trials, RX 238 and 239, failed to include a placebo and one did not include a standard (RX 239).

850. Dr. Carson admitted on cross-examination that he did not

know if Dr. Tainter ever accepted the concept of a factorial design and that subsequent authorizations for each study came individually (Carson, Tr. 16054).

851. Even assuming that the concept of a factorial design was agreed upon, the methodology employed in the studies varies from study to study in several respects so as to preclude "pooling" of the results: (1) The patient population and screening procedures were different in the first two studies. (2) The method of dose administration varied. (3) The formulation of Cope was not the same in all studies. (4) Two of the studies included placebo control and two did not.

852. It is found that RX 236–239, either singly or in combination, are not adequate to support claims of superior therapeutic effectiveness for Cope as a tension headache reliever. The only comparative efficacy studies conducted on Cope (RX 238, 239) do not meet the standards of a well-controlled clinical trial necessary to establish superior efficacy for Cope in relieving tension headache. **[205]**

853. Because the representation has not been established according to the criteria set forth and adhered to by qualified experts in the scientific community, it was made in the face of a substantial question recognized by such experts as to their validity as alleged in Complaint Paragraph 13.

D. *Sterling Did Not Have A Reasonable Basis For Its Claim That Vanquish Is Therapeutically Superior Or That Such Superiority Has Been Scientifically Established*

854. Vanquish contains 227 mg aspirin, 194 mg acetaminophen, 33 mg caffeine, 50 mg magnesium hydroxide and 25 mg aluminum hydroxide gel (Carson, Tr. 15863).

855. Extra ingredients or more of an ingredient is not evidence that can establish Vanquish's superior efficacy over aspirin or any other OTC analgesic.

856. One tablet of Vanquish contains 431 mg of analgesic ingredients (227 mg aspirin plus 194 mg acetaminophen). Respondent's witness Dr. George Goldstein, Vice President and Medical Director of Winthrop Laboratories division of Sterling, that the addition of acetaminophen to aspirin in the dosages contained in Vanquish might provide some individuals with longer duration of effect (Goldstein, Tr. 15624). However, in earlier comments submitted to the FDA's OTC Panel on Internal Analgesics, he asserted that nonstandard dosage forms with larger quantities of analgesics offer no therapeutic advantage over the standard dose of 32 mg of analgesic in a tablet (CX 574C). Moreover, Dr. Goldstein could not cite any clinical evidence to support his opinion given at trial that the added analgesic in Vanquish

might produce a longer duration of effect (Goldstein, Tr. 15628). Dr. Goldstein also represented earlier to the FDA OTC Internal Analgesics Panel that because acetaminophen lacked antiflammatory capabilities, it was not as effective a pain reliever as aspirin (CX 574D). Thus, it would be inappropriate to equate the analgesia produced by acetaminophen and aspirin on a milligram-for-milligram basis.

857. Dr. Trout, Senior Vice President of Medical and Scientific Affairs of Sterling Drug Inc., testified before the FDA's OTC Panel on Internal Analgesics on behalf of Sterling Drug, when the Panel was considering both the use of 325 mg of aspirin as the standard dosage unit and the criteria allowing variation from that standard. After urging a disclosure statement for nonstandard dosage units products which contain additional ingredients or vary from the standard are not superior in safety or effectiveness to 650 mg of aspirin (2 tablets of 325 mg aspirin), he stated: **[206]**

> In support of this requirement of disclosure or proof for all variance from the standard, it should be noted in regard to pain relief that the general scientific consensus is that existing combinations of aspirin with other OTC ingredients and aspirin at higher dose levels are not superior to 650 mg. of straight aspirin. (CX 455K).

858. The addition of buffers to Vanquish does not alone constitute evidence that establishes its superiority over plain aspirin or any other OTC internal analgesic in the relief of pain and was so recognized by respondent (F. 828, *supra*).

859. Caffeine in combination with OTC internal analgesics has not been proven to enhance or potentiate analgesic effectiveness and may be contraindicated because it heightens an individual's awareness of pain (F. 815, *supra*).

860. With respect to mixtures of analgesic and antipyretic ingredients, the 1971 and 1973 editions of the *AMA Drug Evaluations* (CX's 467, 468) concluded that because the rationale for these combinations is open to question, and because adequate studies have not demonstrated their superiority, the use of a single analgesic is preferred (CX 467I, 468G).

861. Respondent offered only one clinical test (RX 224) in support of its claims for the marketed formulation of Vanquish. RX 224 is another FDRL studies designed and conducted by FDRL under contract to Sterling Drug Co. (Glenbrook Laboratories) (Carson, Tr. 15856) and submitted to Glenbrook Laboratories in April 1967 (RX 224A). The protocol was designed by Dr. John Silson, then a clinical consultant to FDRL (Carson, Tr. 15855–56). Dr. Steven Carson administered the protocol and maintained contact with Sterling as to the progress of the study (Carson, Tr. 15851, 15898).

862. According to Dr. Moertel, this study does not meet the requisites of a well-controlled clinical trial. He concluded that the results do not provide any substantive evidence of any therapeutic superiority of Vanquish as compared to aspirin (Moertel, Tr. 6324). The study used a large patient population scattered at a number of industrial plant locations (Carson, Tr. 16002–02). Dr. Carson did not visit any of the sites and did not know whether Dr. Silson had done so (Carson, Tr. 16003–04). Individuals reported to the respective industrial health clinics complaining of headache (Carson, Tr. 16003–03). The screening process did not involve asking the individuals whether they were taking any medication (other than tranquilizers) (Carson, Tr. 16002–03), or whether they had recently taken other analgesics prior to coming to the clinic (Moertel, Tr. 6327; Carson, Tr. 16002–03). Patients were given unmarked medication, **[207]** written instructions or forms to record their responses to treatment. They were asked to report back results the next day, or as soon thereafter as possible (RX 224D). Upon return to the clinics, responses regarding the nature of relief were reported to the nurse investigator from memory (Carson, Tr. 16004). The nurse investigator recorded responses on a precoded questionnaire (Carson, Tr. 16004–05). The medication was dispensed at the time an individual reported headache and there is no data in the report reflecting whether the medication was taken at that time or any other time (Carson, Tr. 16002–03).

863. The patient population had certain characteristics which could have significantly affected the patients' responses to an analgesic drug. These variables were not controlled. Among the three factors which the authors recognized in their report to have had an influence on the response of analgesic agents, aspirin was at a disadvantage (RX 224G,H; Moertel, Tr. 6334). For example, in patients with chronic sinusitis, aspirin had a twelve-patient disadvantage (RX 224P, Table 1; Moertel, Tr. 6333); the aspirin group included more patients with severe headaches than in the Vanquish group and more patients with frequent headaches (RX 224P, Table 1; Moertel, Tr. 6334). All of these factors combine to put aspirin in a more unfavorable light than Vanquish (Moertel, Tr. 6334). The study also failed to find a statistically significant difference between 650 mg of aspirin and placebo (Moertel, Tr. 6326). Based on the data, Dr. Moertel noted that 90% of the individuals reported some degree of relief, ranging from 11% with complete relief to 44% with slight relief with sugar pills (RX 224Q, Table 2). This shows there was a high degree of placebo response (Moertel, Tr. 6330).

864. In any event, the study failed to find a statistically significant difference between aspirin and Vanquish. The authors of the report concluded that the differences in the pain relief index between two

tablets of Vanquish and two tablets of aspirin and between aspirin and placebo did not reach statistical significance (RX 224G). Although more patients claimed complete relief from a first dose of Vanquish as compared to the other two medications (RX 224G), there were also more patients who needed a second dose of medication after taking Vanquish (RX 224T, Table 5; Moertel, Tr. 6336). The study also reported side effects and found no significant differences among the medications (Moertel, Tr. 6337).

865. Also included in the report was a "preference index" (RX 224I). Dr. Carson agreed that a preference index is not a measure of efficacy and is not a component of a well-controlled clinical trial (Carson, Tr. 16007). In any event, in terms of "preference index," the study did not show a significant difference between Vanquish and aspirin.

866. Dr. Carson testified that the FDRL study on Vanquish was carried out in five different plants and therefore afforded [**208**] "instant replication." In fact the data from the five plants were pooled. Although Dr. Carson testified that there were no significant differences among the various groups in the five locations reporting data (Carson, Tr. 16015–16). The final report of this study notes that certain cross tabulations of data by location showed a uniformly lower response on certain parameters at the Vatavia plant. The authors suggest this was due to observer differences (RX 224H).

867. From all of the above, it is found that the FDRL's Vanquish study (RX 224) suffers from serious methodological differences and failed to show a statistically significant difference between Vanquish and aspirin. It is entitled to little weight regarding the issue of Vanquish's therapeutic superiority.

E. *Sterling Did Not Have A Reasonable Basis For Its Claim That Vanquish Causes Significantly Less Stomach Upset Than Any Other OTC Analgesic Product Or That Such Superiority Has Been Established*

868. Vanquish contains 50 mg of magnesium hydroxide and 25 mg of aluminum hydroxide which are recognized as antacid agents (CX 466, p. 35469). An antacid may be defined as "[a]n agent that reacts with acid such as the hydrochloric acid of the stomach (gastric acid), and neutralizes it (decrease the amount)" (CX 466, p. 35373).

869. The buffers in Vanquish, magnesium hydroxide and dried aluminum hydroxide gel, are water insoluble buffering agents (CX 466, p. 35375; Danhof, Tr. 17247). Magnesium carbonate, a water soluble buffering agent has been shown to speed dissolution better than water insoluble agents (CX 466, p. 35375).

870. It has been suggested by some that the presence of antacids of the type and in the amount found in Vanquish may lessen gastric

irritation by speeding the dissolution of the aspirin tablet, and thereby increasing the rate at which aspirin leaves the stomach and is absorbed into the system (Goldstein, Tr. 15684; RX 250–Morgan). This theory is open to serious doubt (Grossman, Tr. 7602, 7608; CX 467G; CX 468H). To the extent the antacids in Vanquish increase aspirin dissolution, the increase is quite small (Grossman, Tr. 7498). The FDA OTC Internal Analgesics Panel has noted that "there is little meaningful difference between the rates of absorption of sodium salicylate, aspirin and the numerous buffered aspirin preparations of salicylates" (CX 466, p. 35378). The disintegration of aspirin depends on many factors besides the action of added buffers; the disintegration and dissolution rate of an aspirin tablet is probably as dependent on the way it is fabricated as it is to added buffers (CX 466, p. 35375), and is also dependent on the amount of food in the stomach and gastric emptying time (CX 466, [**209**] p. 3578; Danhof, Tr. 17248). However, assuming that the rate of dissolution, disintegration and absorption of aspirin is increased by the addition of antacids, there is no clinical evidence linking this phenomenon with a significant decrease in aspirin side effects such as stomach distress (Grossman, Tr. 7493, 7602).

871. Nor could antacids in the amount found in Vanquish be expected to neutralize the acidity of the stomach's contents and thereby lower the incidence of stomach distress associated with aspirin (Grossman, Tr. 7492). The amount of antacid in Vanquish is barely sufficient to neutralize the acidity of aspirin in the product itself, and thus could not significantly decrease, much less neutralize, the acidity of the stomach's contents as a whole (Grossman, Tr. 7493–96). Vanquish could not significantly decrease the damaging effects of aspirin on the stomach because it cannot neutralize the acid in the stomach (Grossman, Tr. 7493). As long as the stomach contents remain even slightly acidic, the aspirin in Vanquish will exert its adverse effects. An effective dose of antacid employed for neutralizing stomach acid has over 250 times as much neutralizing capacity as Vanquish's 75 mg (Grossman, Tr. 7496).

872. Even if the addition of antacids to Vanquish had some effect, it would merely tend to diminish the topical effect of aspirin on the gastric mucosa (Grossman, Tr. 7493). These effects would have no bearing on aspirin's systemic action adverse to the gastric mucosa which occurs after absorption (Grossman, Tr. 7481).

873. Sterling relied upon articles by Gerhard Levy, a well known and respected investigator of the physicochemical characteristics of aspirin products. In an article published in 1960, Dr. Levy noted that "[S]ince the relative incidence of gastrointestinal irritation in normal subjects caused by moderate doses of the drug is quite low, clinically noticeable differences between two products can only be apparent

when there are pronounced differences in the dissolution characteristics of the two products" (RX 250-Levy, Physicochemical, p. 1055).

874. The record does not show that there are "pronounced differences in the dissolution characteristics" between Vanquish and other OTC analgesic products. Instead, Sterling relied on blood level studies, measurements of occult blood loss and clinical trials with Bufferin, a product of different composition and formulation, in an attempt to show that Vanquish is gentler to the stomach than all other aspirin.

875. Respondent also relied upon blood level studies on the precursor formulation to Vanquish. One of these blood level studies was done in 1956 by Dr. Leon Greenberg for Sterling Winthrop Research Institute. Dr. Greenberg carried out a series of four blood level studies on the product Instantin/Falgos (RX [**210**] 222E). The formulation of Instantin/Falgos was similar but not identical to the marketed version of Vanquish. The former contained phenacetin in combination with aspirin, plus caffeine and buffers (RX 222E); Vanquish contains acetaminophen instead of phenacetin. None of Dr. Greenberg's studies were direct comparisons of Instantin/Falgos with plain aspirin or Bufferin. Rather, he compared blood level data from subjects taking Instantin/Falgos with blood level data from subjects who took Bufferin or Bayer three and one-half months earlier (Goldstein, Tr. 15718; RX 223J, K). In the two instances where Instantin/Falgos was compared with Bayer and Bufferin on the basis of earlier data, the amounts of aspirin administered were not equivalent. That is, the aspirin in Instantin was equivalent to 10.5 grains, while that in Bayer and Bufferin was 10 grains (Goldstein, Tr. 15720; RX 222J, K).

876. Two other blood level studies relied upon by Sterling's expert witnesses (RX 250-Morgan and RX 250-Paul) compared blood levels of Bayer Aspirin to Bufferin, which contains different buffering agents than those in Vanquish. The studies included no data on Vanquish or an aspirin product containing the buffers used in Vanquish (Goldstein, Tr. 15686).

877. Sterling also relied upon studies measuring occult blood loss (RX 250-Arviddson; Danhof, Tr. 17249–50). The study by Arviddson compared occult blood loss after ingestion of plain aspirin and a buffered aspirin and found that the buffered aspirin caused less bleeding than the plain aspirin. This study cannot be relied on to draw any conclusions about the relative effect of buffers in Vanquish because (1) the buffered tablet in the study was administered in solution whereas the aspirin product was not and (2) the buffered tablet contained 1250 mg of a water soluble buffer (bicarbonate) — a quantity of buffers over 16 times the amount present in Vanquish. Bicarbonate

is also a different buffering agent from the buffering agents in Vanquish (Danhof, Tr. 17249–50).

878. Even if the occult blood loss data actually had compared Vanquish to aspirin and had shown Vanquish to reduce occult blood loss, the data would not necessarily have clinical significance (Danhof, Tr. 17254), for occult blood loss is not generally associated with any symptoms or disability and is not regarded as clinically significant. It is merely an index of the fact that aspirin does injure the gastric mucosa and causes bleeding (Grossman, Tr. 7480).

879. Sterling also relied on an article by Hoon (RX 250-Hoon) where gastritis was examined with intragastric photography. Neither Vanquish nor products containing buffers in the amount found in Vanquish was involved in these observations. In fact, the formulations tested included buffers in the form of large amounts of antacids (2500 mg of magnesium-aluminum hydroxide in Ascriptin) and antifoaming agents (Danhof, [211] Tr. 17251; RX 250–Hoon, p. 61). These differences would have had a significant effect on dissolution and gastric irritation (Grossman, Tr. 7493).

880. There are no well-controlled clinical studies demonstrating that buffered aspirin, such as Vanquish, causes stomach distress less frequently than plain aspirin (Grossman, Tr. 7497, 7590–92). The existing evidence is equivocal and suggestive at best (Grossman, Tr. 7605). The *Medical Letter* (CX 460) concluded that it has never been established that there is a difference between buffered and nonbuffered aspirin, *inter alia,* as regards incidence of gastrointestinal distress (CX 460B). Two editions of the *AMA Drug Evaluation* (CX 467, CX 468) similarly concluded that controlled clinical studies have not conclusively demonstrated that buffered aspirin will result, *inter alia,* in less gastric upset than plain aspirin (CX 468G; CX 467H). The FDA OTC Analgesics Panel placed the claim that buffered aspirin "may" cause less incidence of gastric intolerance in Category III, concluding that available evidence is insufficient to support the claim (CX 466, p. 35480).

881. Respondent cited a study by Tebrock in which subjects who reported to a number of industrial clinics with ailments for which aspirin was normally prescribed were given Bufferin. They were later interrogated about side effects (RX 250–Tebrock; Goldstein, Tr. 15689). The subjects were asked to compare the side effects experienced after taking Bufferin with the side effects they had experienced after taking aspirin. Thus the Tebrock study does not approach a controlled clinical trial (Danhof, Tr. 17261). First, the study was not double-blinded (Grossman, Tr. 7606). Second, randomization was impossible since the only treatment administered in the study was Bufferin. Third, the subjects in this study were not tested

with aspirin on a blinded basis (Danhof, Tr. 17261). The subjects simply reported the incidence of side effects experienced with 12 tablets of Bufferin (2 tablets every 3 hours) while in the study, and then they were asked to compare this experience with their own recollections of whether they had, at any time in the past, experienced stomach distress which they thought was due to taking plain aspirin (RX 250–Tebrock). This is called a "historical control" (Danhof, Tr. 17260). However, consumers' unblinded perceptions are not evidence that can be used to establish relative performance of drugs, even where the issue involved is side effects (Grossman, Tr. 7888–89). The problems are compounded when a study also requires the subjects to base their unblinded judgments on recollections from the past.

882. The FDA regulations on clinical testing state that meaningful blinding and randomization are among the absolute essentials of adequate and well-controlled clinical investigations (21 C.F.R. 314.111(a)(5)). The FDA regulations allow "historical controls" only where the nature and course of **[212]** the disease being studied, if left untreated or treated by means other than the test treatment, is so well known, predictable and unacceptable that reliance on well-documented historical data for control purposes is the only acceptable alternative to direct comparison in a clinical trial. The FDA cites "the high and predictable mortality" of childhood leukemia as an example where use of a "historical control" would be permissible. *See* 21 C.F.R. 3.14.111(a)(4). Analogous circumstances are not present in determining the incidence of stomach upset caused by aspirin. For all of these reasons, the Tebrock study amounts to little more than a historical survey and falls far short of controlled clinical study (Grossman, Tr. 7606).

883. Respondent also recognized the inadequacy of the Tebrock study in its complaint to the FTC in 1956 regarding certain comparative claims being made for Bufferin by Bristol-Myers (RX 410). At that time, respondent stated that " . . . the techniques he [Tebrock] used scarcely justify any scientific conclusion . . . " (RX 410, p. 44).

884. The Panel Study (RX 250–Paul) cited by respondent also compared Bufferin and aspirin using "historical control." As in the Tebrock study, the investigator was aware of the purpose of the study and the fact that he was administering Bufferin to the test subjects; thus the study was not double-blinded (Danhof, Tr. 17256). Again, only Bufferin was tested in the trial (Danhof, Tr. 17258). Again, a "historical control" was used: subjects' reports of stomach upset with just two tablets of Bufferin were compared with their recollections of whether they had at any time in the past experienced stomach upset they believed associated with the ingestion of plain aspirin (Danhof, Tr. 17256). For these reasons, together with the fact that the study

tested Bufferin, an agent which includes buffers different from the buffers in Vanquish, the Paul study falls far short of a controlled clinical study which provides substantiation for Vanquish's claims of superior gentleness.

885. Furthermore, as in the case of the Tebrock study, respondent vigorously criticized the results of the Paul study in its 1956 complaint to the FTC (RX 410, pp. 21–22).

886. Sterling also cited a study by Fremont-Smith, published in the *Journal of the American Medical Association* in 1955. The study, employing subjects suffering from arthritis, was designed as a long-term crossover study comparing Bufferin and aspirin (Goldstein, Tr. 15692). The long-term portion of the study was an unblinded "open trial," and cannot qualify as a well-controlled clinical study (Grossman, Tr. 7605; Danhof, Tr. 17261). The study itself notes that arthritic patients, who were the exclusive subjects under study, are subject to a variety of gastrointestinal abnormalities. Thus, even if it were otherwise well-controlled, the study would not be applicable to nonarthritics (RX 410, p. 45; Goldstein, Tr. 15692–[213]96). Respondent had criticized Dr. Fremont-Smith's work for just this reason in its petition to the FTC against Bristol-Myers claims for Bufferin (RX 410, pp. 45–48):

> Dr. Fremont-Smith was not attempting in his experiment to compare the intolerance of aspirin to that of Bufferin in the general public. On the contrary, his investigation was designed to determine the incidence of gastro-intestinal intolerance to Bufferin as compared with aspirin in patients with rheumatoid arthritis (RX 410, p. 45).

887. Respondent also relied upon a study by Harris and Bird entitled "Clinical Evaluation of a New Buffered Aspirin, Phenacetin and Caffeine Analgesic," published in *Clinical Medicine,* in 1956 (RX 222Z056). The study was designed to compare Falgos (a precusor formula of Vanquish and containing phenacetin) to plain aspirin in a double-blind study conducted with 25 elderly patients in an infirmary and home for the chronically ill. The study reported greater incidence of side effects following aspirin administration than for Falgos (RX 222Z057). The study itself concludes that it "was somewhat severe one for mild analgesics because of the character and chronicity of most complaints which were treated" (RX 222Z057). Given the particular patient population, it would be important to know whether other medications were controlled for prior to participation in the study (Goldstein, Tr. 15721). The study does not touch on this concern and it is impossible to conclude that any differences in incidence of side effects observed were in fact attributable to Falgos or aspirin alone.

888. Thus, it has not been established that Vanquish is gentler to the stomach than any other plain aspirin (Grossman, Tr. 7497; Com-

plaint ¶ 9). The challenged representation in Complaint ¶ 8(B)(2), that it has been established that because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any nonprescription internal analgesic not containing buffers, is therefore false. Furthermore, because the representation has not been established according to the criteria set forth and adhered to by qualified experts in the scientific community, they were made in the face of a substantial question recognized by such experts as to their validity as alleged in Complaint ¶ 13.

F. *Sterling Did Not Have A Reasonable Basis For Its Claim That Vanquish Is A More Effective Pain Reliever Than The Largest Selling Extra Strength OTC Analgesic Product Or That Such Superiority Has Been Established*

889. Two well-controlled clinicals are required to establish the therapeutic superiority of one drug over another (F. 421, *supra).* **[214]**

890. At the time the challenged claims for Vanquish were made, Anacin (which combines 400 mg of aspirin with 32.5 mg of caffeine per tablet) was the largest selling extra strength pain reliever (CX 678, admission 403).

891. Respondent presented no clinical or other *in vivo* data comparing Vanquish to Anacin for relief of pain. Therefore, it has not been established that Vanquish is a more effective pain reliever than the largest selling extra strength OTC analgesic as alleged in Complaint ¶ 12C.

892. From the foregoing, the various establishment claims regarding Bayer Aspirin, BCA, Vanquish and Cope, discussed in A through F, *supra,* were false because of the existence of a substantial question regarding the validity of such claims, as alleged in Complaint Paragraphs 9 and 13, and respondent's failure to disclose the existence of such substantial questions constituted a failure to disclose material facts, as alleged in Complaint Paragraph 14.

G. *Bayer Aspirin And The Ingredients In Cope Or Midol Do Not Relieve Tension*

1. Introduction

893. Tension (often used synonymously with "stress") is a term for one of the symptoms of a general state of anxiety (Rickels, Tr. 7910–11, 8188; Fields, Tr. 16609). This anxiety syndrome encompasses other symptoms which also may accompany tension, such as irritability, worry, heart palpitations, headaches, and perspiration (Rickels, Tr. 7910, 7911, 7962). Tension also is a term which is used to describe a state of muscles (Rickels, Tr. 7910–11).

894. Tension can be appropriately treated by nondrug methods, such as psychotherapy or psychiatric counselling. It also can be appropriately treated with anti-anxiety drugs or tranquilizers (Rickels, Tr. 7910–11, 8013). Anti-anxiety drugs or tranquilizers are psychotropic drugs, *i.e.*, agents which affect the psyche, or emotional and intellectual functions as governed through the cerebral mechanism (Rickels, Tr. 7897–98; G. Goldstein, Tr. 15050–51; L. Goldstein, Tr. 17761).

895. Sterling Drug, Inc. made claims in advertisements that a recommended dose of Bayer Aspirin, Cope, or Midol will relieve tension, anxiety and irritability, and enable persons to cope with the stresses of everyday life. Sterling made such claims for Bayer Aspirin from July 1969 up to at least June 1971 (CX 630). Sterling made such claims for Cope from January 1969 up to at least June 1971 (CX 633). Sterling made such claims for Midol from December 1966 up to at least November 1973 (CX 634). **[215]**

896. The active ingredient in Bayer Aspirin is aspirin. The ingredients in Cope are aspirin, buffers, and methapyrilene fumarate. The ingredients in Midol are aspirin, caffeine, and cinnemadrine hydrochloride. None of these ingredients, either alone or in combination, are considered to be effective antianxiety agents or tension relievers, nor will they enable persons to cope with the ordinary stresses of everyday life. Caffeine, an active ingredient in both Cope and Midol, is actually contraindicated for the treatment of tension.

897. The FDA OTC Nighttime Sleep-Aid, Daytime Sedative and Stimulant Products Panel examined products which, among other things, were sold to provide relief for "nervous tension," "nervous irritability," "nervousness due to common everyday overwork and fatigue" (Rickels, Tr. 7983; CX 465A, pp. Z004, Z005). Aspirin was an ingredient in some of the products the Panel reviewed with respect to such claims (Rickels, Tr. 7986; CX 465A, pp. Z004, Z005). However, no company made a submission to the Panel claiming that aspirin alone could provide relief for these symptoms. Instead, the materials provided by manufacturers regarding drugs that included analgesics as component ingredients claimed only that the analgesics were included solely for their analgesic action (Rickels, Tr. 7984). The Panel concluded that aspirin was ineffective for relieving nervous tension (Rickels, Tr. 7984; CX 465A, pp. Z005–Z005). The Panel also concluded that "everyday tension," "nervousness" or "stress" [for which Sterling claims aspirin provides relief] represents "normal or relatively normal variations in mood [which are] probably not . . . appropriate . . . for pharmacological intervention" (Rickels, Tr. 7983, CX 465A, p. Z005).

898. The FDA OTC Sedative Panel based its decision, in part, on a study entitled, "Over-the-Counter Sedative, A Controlled Study" (CX

518) which was co-authored by the Chairman of the Panel, Dr. Karl Rickels, a witness in this proceeding and a well-recognized expert in clinical psychopharmacology. CX 518 was a well-controlled, double-blinded clinical study of Compoz, librium, aspirin, and placebo in patients suffering mild to moderate degrees of tension (Rickels, Tr. 7944–45, 7974–78; CX 518, p. 31; CX 465A, p. Z003). Compoz—sold as a daytime sedative—consisted of .15 mg of scopolamine (an agent which affects the nervous system); 25 mg of antihistamine (methapyrilene hydrocholoride and pyralamine); 120 mg of salicylamide (an analgesic); and 7.5 mg of passion flower. The aspirin doses were 500 mg, three times daily, slightly less than the usually recommended dosage of aspirin. The study concluded that Compoz and aspirin were no more effective as tension relievers than a placebo and that all three were significantly less effective than librium (Rickels, Tr. 7951–52; CX 465A Z003). This result is consistent with the credible scientific literature regarding the lack of tension relieving properties of aspirin (Rickels, Tr. 7952).

899. Michael Gilbert and Hans Koepke conducted a study that corroborates the conclusion of Dr. Rickels' study that aspirin **[216]** has no tension-relieving properties. This study was a controlled clinical trial credited as an excellently designed study by Dr. Rickels and authorities at the Food and Drug Administration (Rickels, Tr. 8181). The study involved a test of aspirin and meprobamate (a minor tranquilizer) in 188 patients being treated for muscular skeletal pain and cramps associated with anxiety and tension (Rickels, Tr. 8173, 8188, 8195). The dosage of aspirin consisted of two tablets (650 mg), three times daily (Rickels, Tr. 8973). The study concluded that the aspirin at this dosage level did provide pain relief, but offered no relief of anxiety apart from the relief of pain (Rickels, Tr. 8051, 8175, 8195).

900. Dr. Rickels testified that there are no clinical tests involving the administration of aspirin at greater than the 2-tablet (650 mg) dose which have shown that aspirin has any tension-relieving properties (Rickels, Tr. 8197–98). He also added that aspirin in the amount of 3900 mg/day (or 2 tablets consisting of 650 mg 6 times/day) would not be useful as a daytime relaxant since a patient would have to be awakened at night to continue taking two pills every four hours (Rickels, Tr. 8197).

901. The conclusion of the FDA OTC Internal Analgesics, Antipyretic and Antirheumatic Products Panel is in accord with the conclusions reached by the OTC Nighttime Sleep Aid, Daytime Sedative, and Stimulant Products Panel. The Internal Analgesics Panel concluded that nonprescription internal analgesics are "clearly ineffective" for "nervous tension" (CX 466, p. 35355).

902. As of mid-May 1969 Sterling was aware that aspirin and caf-

feine were not regarded by the scientific community as tension-relieving agents. At that time, Bristol-Myers, a Sterling competitor, made tension relief claims for Excedrin (CX 358). Sterling knew these claims were based on evidence which would not be regarded by the scientific community as adequate evidence because of the absence of any well-controlled, clinical, double-blinded, placebo test using a sufficiently large, randomly selected population (CX 358).

903. Respondent presents no evidence that caffeine, an active ingredient in Midol and Cope, produces any tension-relieving properties in these products. A combination of caffeine with aspirin or in combination with other OTC ingredients (including those in Midol and Cope) is not effective for treatment of nervous tension (Rickels, Tr. 8020–21). Indeed, caffeine is contraindicated for the treatment of tension (Rickels, Tr. 7974).

904. Respondent presents no evidence that buffers, an active ingredient in Cope, produce any tension-relieving properties. Instead, Sterling's evidence with regard to buffers is that addition of the buffers may help prevent possible gastric upset. The administration of a buffering agent is not [217] indicated for relieving tension or anxiety (Rickels, Tr. 7974). A combination of buffering agent(s) with aspirin does not make that drug or drug containing aspirin such as Cope any more effective in relieving tension or anxiety: The buffering agent merely functions to make that drug possibly more acceptable to persons with upset stomach reactions to analgesics (Rickels, Tr. 7975).

905. Cinnamedrine hydrochloride, an active ingredient in Midol, is a uterine antispasmodic which acts to relieve muscle cramps (Rickels, Tr. 8020; R. Hartmann, Tr. 9137; G. Goldstein, Tr. 15547). This ingredient has no effect on nervous tension (Rickels, Tr. 8019; G. Goldstein, Tr. 15549). A combination of this ingredient with aspirin and caffeine also has no effect on nervous tension (Rickels, Tr. 8019).

2. Aspirin Has No Tension-Relieving Properties

906. Headache pain can be a symptom of tension. In such instances, the headache pain is caused by the underlying tension or stress (Rickels, Tr. 7961–62, 8098; CX 465A, p. 57320).

907. Headache pain also can be a cause of tension. Such headache pain may itself be either the direct result of preexisting tension and stress, or the headache may exist independently of, though simultaneously with, the underlying tension (Rickels, Tr. 8103). In the latter instance, the headache is caused by something other than the underlying tension, *e.g.*, environmental factors such as certain gases or toxic substances (Rickels, Tr. 8103). Regardless of its cause, the headache pain may act to aggravate preexisting tension, *i.e.*, to increase the level of preexisting tension (Rickels, Tr. 7962–63, 8100).

908. In those instances when an individual is suffering from tension which causes a headache as one of its symptoms, aspirin is neither appropriate nor indicated for the treatment of the underlying tension. As an analgesic, aspirin will relieve the pain of the headache and, because that pain is gone, much of the tension that was caused by the pain may be lessened. But aspirin will never treat the tension that caused the headache in the first place (Rickels, Tr. 7963–64).

909. Where one has a headache without preexisting tension and then gets tense, nervous, or irritable because of the headache, aspirin will make the tension go away because it relieves the cause: the headache (Rickels, Tr. 8101). However, that does not mean aspirin can be described as having tension-relieving properties. Dr. George Goldstein, respondent's medical director, agreed that the psychotropic effect of aspirin in relieving pain is only "indirect" or "associated" (G. Goldstein, 15051, 15548–49). That kind of "associated" effect [**218**] does not support claims that a product has tension-relieving properties. Dr. Rickels gave an analogy to illustrate this point: A person with a bladder infection who has to frequently urinate may awake during the night. By taking an antibiotic which cures the infection, that person can enjoy a full night's sleep again. The antibiotic, however, cannot be called a sleep-aid merely because it cured the disease that resulted in sleeplessness (Rickels, Tr. 8102–03). Dr. Goldstein agreed with this rationale with regard to sleep aids (G. Goldstein, Tr. 15551–53). The same logic, however [as Dr. Rickels testified], applies equally to claims for tension relief (Rickels, Tr. 8102–03).

910. Unlike claims related to aspirin's use for pain relief, inflammation, and fever, tension-relieving claims for aspirin are novel, not well-recognized, and are not supported by clinical trials reported in the medical literature (Robert John, Tr. 5675–76; Scoville, Tr. 14527). Thus, tension relief claims for aspirin must be independently substantiated (R. John, Tr. 5675–76). In determining that there is reason to believe that a drug has tension-relieving properties, information derived from well-controlled, randomized, double-blinded clinical studies in a well-defined population is given the most weight by scientists (Rickels, Tr. 7932–40, 7965, 7978–79, 8037). In addition to the independent scientific community, the pharmaceutical industry generally, and Sterling in particular, has also recognized that clinical tests are preferred evidence to substantiate any efficacy claim, including a tension-relieving claim (R. John, Tr. 5508–09, 5511; F. 442–448, *supra*).

911. Sterling relied for its claim that aspirin has tension-relieving properties on various studies and reports in the literature. These materials were discussed by Dr. G. Goldstein and Dr. L. Goldstein and include: (1) a study by Krumholtz and Merlis, entitled "Studies with

Acetylsalicylic Acid," (1965); (2) a 1959 report by Boyd, Huppert, Sullivan, and Molinus, entitled "Hypnotic Effects of Bufferin" (1959); (3) various reports in the literature which are based on observations rather than tests or studies, including comments by Dr. Gold appearing in an article, "Therapeutics, Conferences on Therapy" (1942), comments by Dr. Wolff appearing in "Psychologic Aspects of the Treatment of Pain" (1945), and comments by Dr. Paul appearing in "Aspirin For Insomnia" (1956); (4) a chapter in a 1969 medical textbook, entitled "Use of Drugs in Relief of Pain" by Arthur Grollman; (5) various electoencephalogram studies, including three studies by Pfeiffer and Goldstein, "Quantitative Electroencephalographic Analysis of the Effects of Aspirin in Man" (1965), "Bioassay of Different Formulations of Aspirin by Means of the Human EEG (1967)" and "Electroencephalographic Assay of Anti-Anxiety Drugs" (1964); and an abstract of the studies reported by Goldstein and Pfeiffer, entitled "Anti-Anxiety (EEG) Effects of Aspirin and Congeners in Man" (1966); a study by Fin, "EEG and Human Psychopharmacology" (1969), and a study by Hauri and Silverfarb, "Effects of Aspirin on the Sleep of Insomniacs" [219] (1978); (6) reports on the effect of tryptophan on sleep, including Aylward's letter to the editor of *Lancet,* "Plasma Level in Depression" (1973); Hartmann's article "L-Tryptophan: A Rational Hypnotic With Clinical Potential" (1977); and an article by Smith, "Effects of Acetylsalicyclic Acid on Serum Protein Binding and Metabolism of Trypotophan in Man" (1971).

912. The record does not reflect any study funded by Sterling to determine or evaluate the amount or degree of tension relief afforded by aspirin until Glenbrook co-funded the 1978 Hauri Study (L. Goldstein, Tr. 17856). This study post-dated respondent's advertising claims.

913. The 1965 Krumholtz and Merlis Study, "Studies With Acetylsalicylclic Acid" attempted to answer the question whether aspirin, caffeine, or phenacetin alone can reduce fearfulness and depression (L. Goldstein, Tr. 17857). The study compared aspirin, an aspirin compound, a mild tranquilizer, and a placebo on 20 volunteer subjects, ranging from ages 21–63 years. The author concluded that the data supported a conclusion that aspirin alone effected depression and fearfulness (L. Goldstein, Tr. 17857). This study, however, was not conducted in a manner to yield what experts in biomedicine generally regard as acceptable scientific evidence (Rickels, Tr. 8128–30). The study failed to clearly define the symptoms of the test population. Because the authors did not indicate whether all or any of the subjects had headaches, it is possible that the changes recorded in the test subjects may have been related solely to the analgesic effect of the aspirin (Rickels, Tr. 8114–16). Further, the study utilized the Clyde

Mood Scale as a means of evaluating the effect of aspirin on the moods of individuals. This scale is at best of limited validity (L. Goldstein, Tr. 17973). Additionally, the study nowhere indicates that it was designed to test tension-relieving properties of aspirin as well as aspirin's effect on depression (Rickels, Tr. 8115; Goldstein, Tr. 17857). Finally, the authors themselves recognized the deficiencies of their data, concluding that further study, specifically a simple double-blind study with larger groups, was necessary to test the tranquilizing action of aspirin (L. Goldstein, Tr. 17977).

914. The 1959 report, "Hypnotic Effects of Bufferin" by Boyd, Huppert, Sullivan, and Molinus does not provide reasonable scientific evidence in support of their conclusion that Bufferin had hypnotic (sleep-inducing) effects. The study was published in *Medical Times,* 1959. *Medical Times* is not a peer-reviewed scientific journal (L. Goldstein, Tr. 17860–61). This study involved 102 patients who had trouble falling asleep or staying asleep. They were tested either with Bufferin or a placebo in doses of one to four tablets. The patients reported on their subjective feelings. Attendants also described the patient's symptoms (L. Goldstein, Tr. 17859). The authors concluded that Bufferin in a dose of one to four tablets, acted as an effective **[220]** hypnotic in insomnia not due to pain or other physical discomfort (L. Goldstein, Tr. 17860). However, the authors' conclusion that Bufferin had a hypnotic (sleep-inducing) effect should not be credited due to a number of serious methodological flaws in the study. The authors tested 102 patients who provided over 300 responses. Instead of deriving a mean score for each patient and comparing these means, the authors analyzed the data as if 300 patients participated in the study. Such analysis is an error in statistical analysis and is a major flaw in the study because it may affect the results (Rickels, Tr. 8178–79). Further, the study indicated that the majority of test subjects were receiving medication at the time the test was administered, *i.e.,* 42 were taking barbiturates (a sleep-inducing drug), and 9 were taking chloralhydrate (a drug used for its calming effects) (L. Goldstein, Tr. 17981). Because the authors do not state that the test subjects taking concurrent medication (in addition to the Bufferin) at the start of the study, ceased taking that other medication during the course of the study, it may well be that the reported hypnotic effects came from the barbiturates or chloralhydrates and not from the aspirin (L. Goldstein, Tr. 17979–81). Finally, "insomniac" refers to a broad category of persons who cannot sleep for a wide variety of reasons (L. Goldstein, Tr. 17900). The record nowhere states that the insomniacs in this study were suffering "mild anxiety" or "mild tension." Consequently, conclusions regarding the effects of aspirin on insomniacs in this study

cannot be the basis of any conclusions regarding aspirin's effect on tension or anxiety.

915. Sterling relied on various EEG studies as supporting its tension relief claims. EEG studies record brain wave patterns and involve the comparison of the mean energy content (reflected in the average number of pulses per unit time), and the variability of this mean, for test drugs compared to results of various drug groupings, *i.e.,* tranquilizers as having one grouping, sedatives, another grouping. Because the EEG studies do not measure the subjective variables at issue (Rickels, Tr. 7970; Feinstein, Tr. 16441–44), EEG patterns at best only suggest preliminary indications that a drug may have psychotropic effects (Rickels, Tr. 8184–85). EEG studies thus provide data which can be characterized as complementary (L. Goldstein, Tr. 17943), but as recognized by the FDA OTC Panel on Sleep-Aids, Daytime Sedatives and Stimulant Products, results of EEG studies cannot stand alone (L. Goldstein, Tr. 17987). Consequently, in any evaluation of a drug for daytime tension, there must be clinical studies along with EEG studies.

916. Since the inception of EEG studies in the 60's, controversy has existed in the scientific community about the propriety of drawing conclusions about the psychotropic effects of drugs solely from EEG studies (Rickels, Tr. 7971; L. Goldstein, Tr. 17943–45). First, EEG changes may be recorded where no clinical efficacy for humans can be established, while [221] the EEG may record changes suggesting a psychotropic effect of a drug, clinical tests have not been able to demonstrate any clinical efficacy of the drug compared with placebo. A number of drug studies for geriatrics have demonstrated this limitation of the EEG (Rickels, Tr. 8184–85). Second, as Dr. L. Goldstein admitted, dissociation may exist between EEG results and clinical behavior, *i.e.,* an EEG pattern may indicate a person is asleep whereas the subject is actually awake (L. Goldstein, Tr. 17948–50, 17984). Third, EEG results may be misleading because of the variability among test subjects and within test subjects (L. Goldstein, Tr. 17961).

917. Sterling knew that EEG analysis of drugs was controversial in April of 1966 when Franklin Rosenberg, section head of Pharmacology for Sterling, visited Dr. Leonide Goldstein to discuss his studies (RX 148, p. 1). Mr. Rosenberg described the EEG studies as "a fairly new and still very controversial technique" (RX 148, p. 1). After Mr. Rosenberg's visit with Dr. L. Goldstein, the possibility of employing Dr. L. Goldstein to conduct EEG research regarding antianxiety and antidepressant properties of aspirin was discussed. However, Sterling did no EEG studies until the 1978 Hauri and Silverfarb study (L. Goldstein, Tr. 17888, 17892; RX 250–Chase).

918. As to the issue of the variability within each test subject,

results of a study may be affected by the subjective state of the test subjects, including the joys and stress of everyday life (Goldstein, Tr. 17941, 17961–64). This limitation of EEG studies was known by the scientific community when EEG studies began to be used in an attempt to identify psychotropic effects of drugs (Goldstein, Tr. 17937). Dr. Goldstein also criticized the methodology employed in early EEG studies which includes his 1964 study, "Electroencephalographic Assay of Anti-Anxiety Drugs" as well as his two studies on the psychotropic effects of aspirin, "Biassay of Different Formulations of Aspirin by Means of Human EEG," and "Quantative EEG Analysis of the Effects of Aspirin in Man" as well as Dr. Fink's article," EEG and Psychopharmacology" because these early studies did not control for the variability among the test subjects (L. Goldstein, Tr. 17959). These studies were all offered by Sterling as contributing to its reasonable basis for tension relief claims. Dr. L. Goldstein described the evidence in these early EEG studies as "mixing apples and oranges and expressing their averages in terms of bananas." (Goldstein, Tr. 17959). He made this statement on the basis of scrutinizing EEG data and discovering that not controlling for variability among test subjects and within a test subject could result in diametrically opposed results (L. Goldstein, Tr. 17959). He acknowledged this variability could have been controlled, in part, merely by eliciting subjective information from the test subjects participating in these earlier studies (L. Goldstein, Tr. 17960–61). Dr. Goldstein has not performed any study to determine whether tests would show any psychotropic effect of aspirin when [222] the variability in test subjects was controlled (L. Goldstein, Tr. 17964). Additionally, he testified that EEG techniques have been refined to better accommodate variability; *i.e.,* data is now collected by placing electrodes on both hemispheres of the brain rather than the earlier method of placement of the electrodes solely on the left hemisphere of the brain. Dr. Goldstein admitted he has not utilized this more refined technique to determine whether EEG studies would show any psychotropic effect of aspirin (L. Goldstein, Tr. 17964).

919. As to the two aspirin studies Dr. Goldstein co-authored, the most serious criticism of the 1965 study (which applies equally to the 1967 study) was, as Dr. Goldstein admitted, that antianxiety effects were being measured in subjects who were not experiencing anxiety (RX 250–Pfeiffer–65). Sterling was aware in April of 1967 that both Dr. Goldstein's aspirin studies failed to test a population of mildly anxious (or midly depressed) test subjects, a failure which they characterized as "unfortunate" (RX 148, p. 1). Dr. Goldstein gave a practical rationale for this failure of his studies: The symptoms of the population of the persons for which he was testing aspirin's effect,

depression and anxiety, were ". . . ill defined and transient" (RX 250–Pfeiffer–65). Dr. Goldstein's admission that persons suffering "mild anxiety" or "mild depression" suffered symptoms he characterized as "transient" is a factor discussed by the FDA OTC Sedative Panel as one of the reasons no significant differences could be shown between aspirin and placebo in treating tension (Rickels, Tr. 8142).

920. The EEG study Sterling partially financed, "The Effects of Aspirin on the Sleep of Insomniacs," by Hauri and Silverfarb (RX 250–Chase), published after the period of respondent's tension claims, does not corroborate by any reasonable scientific evidence the claim that aspirin has tension-relieving properties. That study involved eight insomniacs who received either 650 mg of aspirin or placebo (RX 250–Chase; L. Goldstein, Tr. 17897). The study utilized the protocol developed by Kales, et. al. in which aspirin and placebo were administered to each subject alternately in laboratory and outpatient settings (L. Goldstein, Tr. 17891). The authors concluded that 650 mg of aspirin lengthened the total sleep time without significantly changing the duration of the different stages of sleep and also reduced sleep latency, the time necessary to fall asleep (L. Goldstein, Tr. 17897–98). The authors also observed that there were individual differences among the subjects, *i.e.,* only some of the eight benefitted. Two did not benefit at all (L. Goldstein, Tr. 17900; Rickels, Tr. 8127). Dr. L. Goldstein concluded that this wide variability among test subjects was probably due to the fact that "insomniacs" refers to a category of persons who for *many* different reasons cannot sleep (L. Goldstein, Tr. 17900). Therefore, conclusions about the psychotropic effect of aspirin [**223**] based on this kind of data become untrustworthy because the data does not reflect whether the insomniacs may have been unable to sleep because of aches and pains. If all or some of the subjects had pain, then the aspirin as an analgesic may have alleviated or reduced the pain (the cause of the insomnia), enabling the subjects to sleep again. Such an effect does not make aspirin a sleep-aid. Dr. Rickels further criticized the Hauri study because of its use of the Kales protocol. Because the investigators using this protocol knew the sequence of the administration of the treatments to the subjects, the study was not double-blinded (Rickels, Tr. 8125–26), an indispensable feature of well-controlled clinical testing.

921. The Gold, Wolff and Paul comments, as well as the Grollman chapter in the medical textbook, do not provide reasonable scientific evidence supporting the efficacy of aspirin as a tension reliever. It is impossible to determine from Dr. Gold's remarks regarding the sedative effects of aspirin whether he is referring to the direct of indirect effects of aspirin (L. Goldstein, Tr. 17849, 17983–84). Similarly, there is no indication in the record that Dr. Wolff's comments that aspirin

both effects mood by creating feelings of contentment and detachment and induces feelings of sleepiness and relaxation refer to the indirect or direct effects of aspirin (L. Goldstein, Tr. 17850–51). Dr. Paul's remarks that two aspirins taken at bedtime tend to induce sleep and that aspirin could be used in place of sedatives and barbiturates to combat insomnia (L. Goldstein, Tr. 17852) is anecdotal evidence. It does not include any underlying data on what kinds of "favorable effects" occurred or on what patients, *i.e.,* his patients may have been unable to sleep because they were in pain (L. Goldstein, Tr. 17982). Grollman, in his chapter in the 1969 medical text, stated that the sedative and soporific effects of aspirin may contribute to alleviating pain (Goldstein, Tr. 17853). Statements from medical textbooks are not generally accorded much weight as evidence in support of medical claims in the pharmaceutical industry, generally, and by Sterling in particular (Robert John, Tr. 5508–09). The FDA Panel on OTC Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products, in considering textbooks, looked to see if the text referenced a source. Where the source was based on a well-controlled study, the Panel would use the source and not the text (Rickels, Tr. 7978).

922. The effect of aspirin in increasing the level of free tryptophan in the body is no basis for claims that aspirin can reduce tension. Tryptophan is an amino acid which is necessary for the synthesis of serotonin, a chemical whose presence in the brain is necessary for the inception of sleep (L. Goldstein, Tr. 17908–09). All living matter contains some amounts of tryptophan but when it is ingested, it is in bound form. Tryptophan must be in free form for the synthesis of serotonin *Id.*). Dr. Leonide Goldstein, respondent's witness, admitted [**224**] that "the tryptophan-release hypothesis is very appealing because it gives such a nice rationale to the whole story. But I am not naive enough not to know that there may be other mechanisms" (L. Goldstein, Tr. 18015). Dr. Goldstein agreed that the mechanisms (other than aspirin's tryptophan effect) by which aspirin may have a hypnotic effect include aspirin's antipyretic effects, or aspirin's effect on the prostalglandins "or other as yet unexplored avenues" (L. Goldstein, Tr. 18014).

923. Animal studies have shown that the ingestion of large amounts of carbohydrates has increased the blood levels of tryptophan and increased the rate at which the brain synthesizes serotonin (L. Goldstein, Tr. 17989–90). However, Dr. L. Goldstein, would not, on that basis, characterize carbohydrate as having hypnotic effects (L. Goldstein, Tr. 17990). By the same rationale, aspirin should not be characterized as having psychotropic effects merely because ingrestion of large amounts of aspirin in man has increased blood levels of tryptophan.

924. Dr. George Goldstein, Sterling's medical director, stated that the literature was not sufficient to allow him to make a judgment that aspirin had an effect on moods by means of changing tryptophan levels in the body (G. Goldstein, Tr. 15558–61). Dr. Leonide Goldstein, another Sterling witness, admitted he had no knowledge how much free tryptophan must be available to initiate the process of serotonin synthesis. He also did not know how much free tryptophan may result from ingesting given amounts of aspirin (L. Goldstein, Tr. 18037). He further admitted that none of the studies relied upon by respondent establishes a correlation between the amount of trytophan freed by aspirin and the amount necessary to reduce sleep latency (L. Goldstein, Tr. 18008–09).

925. Beefsteak and milk both contain high quantities of tryptophan and by eating these foods, a person could augment his level of free tryptophan (G. Goldstein, Tr. 15566). Other variations in the diet could affect the brain (L. Goldstein, Tr. 17990). Dr. George Goldstein agreed that the design of a study investigating the role of tryptophan must control dietary intake of the subjects to rule out this factor as an operating condition (G. Goldstein, Tr. 15572).

926. The studies cited by respondent reporting the effect of tryptophan on sleep do not constitute reasonable scientific evidence to support claims that aspirin is effective as a tension reliever. Ernest Hartmann's "L-Tryptophan: A Rationale Hypnotic With Clinical Potential" (1977) postdates the period that respondent disseminated tension relief claims. The study consists of seven human studies and one animal study involving the oral administration of tryptophan at high doses (1–15 gm) (L. Goldstein, Tr. 17913–14). Mr. Hartmann concluded that tryptophan reduced sleep latency up to 50% or more as well as [225] increased sleep time of the subjects. This study suffers from a number of flaws. First, Mr. Hartmann does not control for diet (L. Goldstein, Tr. 18003). Second, the subjects in studies 3, 4, 5, and 8 were not insomniacs (L. Goldstein, Tr. 17993). Dr. L. Goldstein testified that insomniacs were the proper population for any studies for sedative effects (L. Goldstein, Tr. 17993).

927. The Aylward Study, "Plasma-Tryptophan Levels in Depression," was published in *Lancet* in April of 1973. This article postdates the period for which respondent disseminated tension claims, with the exception of a few months for the Midol claims. The Aylward Study involved subjects who suffered from rheumatoid arthritis who consumed massive doses of aspirin (eight 2-tablet doses) daily for 28 days (G. Goldstein, Tr. 15574, 15576). Additionally, all the test subjects took paracetamol (acetaminophen) (G. Goldstein, Tr. 15576). Aylward observed in the letter that aspirin increases the tryptophan level in the brain (L. Goldstein, Tr. 17916). The Aylward letter does

not indicate that diet was controlled (G. Goldstein, Tr. 15573). At any rate, Dr. G. Goldstein admitted that this study provided no basis for Midol's mood claims. He stated that a comparison of Aylward's Study with consumers' use of Midol would be "comparing apples and pears" (G. Goldstein, Tr. 15576).

928. Smith in his article, "Effects of Acetylsalicylic Acid on Serum Protein Binding and Metabolism of Tryptophan in Man," (1971) reported that following the administration of 1800 mg aspirin there was a doubling of the amount of free tryptophen in the blood serum and a compensatory 47% decrease in the bound tryptophan (L. Goldstein, Tr. 18036–38). The Smith Study, however, did not control for diet (L. Goldstein, Tr. 18038). Further, while the study reported an increase in the free tryptophan found in the blood serum, conclusions regarding these results are unclear since the record does not reflect, nor did Dr. Leonide Goldstein know, whether it is necessary to have the free tryptophan in the blood or in the cerebrospinal fluid in order to reduce sleep latency (L. Goldstein, Tr. 18009).

929. In contrast to the above studies which did not control for diet, a study by Ian Oswald and Kristine Adam "Lack of Effect of Tryptophan on Sleep Onset Latency" (1979) did control for diet. That study involved the administration of 1 gm of tryptophan 20 minutes before bedtime to 12 subjects suffering from mild insomnia (L. Goldstein, Tr. 17998–99). The subjects ate a high carbohydrate meal on two nights and a low carbohydrate meal on the other nights. The authors concluded that neither tryptophan nor diet had any effect on reducing sleep latency (L. Goldstein, Tr. 18000).

930. The testimony of Dr. George Goldstein and Dr. Leonide Goldstein and materials offered by respondent Sterling are not sufficient to substantiate claims that aspirin can relieve nervous tension. The research studies by Krumholtz, *et. al.* and [**226**] Boyd, *et. al.* had serious methodological effects and cannot be considered to be well-controlled clinical studies. In contrast, the Compoz study by Dr. Rickels and the meprobamate study by Gilbert and Koepke are two well-controlled double-blinded clinicals which demonstrated no significant difference between aspirin and placebo in treating anxiety and stress. The EEG studies presented by Dr. L. Goldstein also provide insufficient evidence to support a claim that aspirin has tension-relieving properties. EEG test results must be viewed cautiously because of the possibility of misleading results due to disassociation between behavior and EEG results and because EEG results may support conclusions where no clinical efficacy can be demonstrated. Additionally, precise definition of the subject population is essential in EEG tests because of the extreme sensitivity of the EEG to variability. However, none of the studies about which Dr. Goldstein testified controlled for

variability. As to Dr. Leonide Goldstein's EEG aspirin studies, as Sterling was well aware, these tests did not involve subjects who were mildly, or moderately, anxious. Therefore, his tests' conclusions are not helpful in terms of nervous tension relief claims. The Hauri and Silverfarb study also is not support for tension relief claims since it involved insomniacs and not anxious persons. As to the tryptophan effects of aspirin, both Dr. Leonide Goldstein and Dr. George Goldstein agreed that the literature was insufficient to support a claim that aspirin could effect moods by means of changing the trypophan levels in the body. Additionally, the literature which they presented on this subject failed to properly control for diet, a factor which may have affected test results. Further, none of these reports or studies provided evidence of a correlation between the amount of tryptophan freed by aspirin and the amount necessary to reduce sleep latency or increase the duration of sleep. The other evidence offered by respondent was anecdotal or in the form of excerpts from texts, evidence generally considered credible by the scientific community or the pharmaceutical community, including Sterling, only when their references are.

931. In contrast, it was the testimony of one of the country's foremost experts in psychopharmacology, Dr. Rickels, that the available scientific evidence does not support any tension-relieving claim for aspirin, a conclusion also reached by both the FDA Internal Analgesic Panel and the FDA Nighttime, Sleep-Aid, Daytime Sedative and Stimulants Product Panel. Thus, as alleged in paragraph 16, during the time respondent disseminated tension relief claims for Midol, Cope, and Bayer, as alleged in Paragraph 15 of the Complaint, there was no reasonable basis for such claim on the basis that aspirin (or aspirin and caffeine) had tension-relieving properties.

3. Methapyrilene Fumarate Is Not A Tension Reliever In Humans

932. Methapyrilene fumarate, an active ingredient in Cope, is an antihistamine (Rickels, Tr. 7946, 8161; John, Tr. 5526). [227] Antihistamines are hypnotic agents which may produce drowsiness or sedation (Rickels, Tr. 8161). However, antihistamines generally and methapyrilene fumarate specifically have not been shown to possess even mild antianxiety properties (Rickels, Tr. 8015–16, 8021–22, 8192–93). A hypnotic agent, such as methapyrilene fumarate, which only produces drowsiness as an effect without any antianxiety effects is contraindicated for daytime relief of tension and anxiety since such an agent might cause a person to fall asleep during the day. This could result in an accident or other adverse situations (Rickels, Tr. 8192). In fact, as of 1972, Cope contained a warning label to the effect that, "This preparation may cause drowsiness. Don't drive a car or operate

machinery while taking this medication" (G. Goldstein, Tr. 15749). Consequently, methapyrilene fumarate is contraindicated for tension relief (Rickels, Tr. 8192–93).

933. Dr. Robert John was medical director of Glenbrook Laboratories Division of Sterling from 1971–1974. During that time he compiled an advertising claim substantiation folder for each product (Robert John, Tr. 5514–15). He also would go through the materials in Sterling's library to find support for specific advertising claims (John, Tr. 5515). He did not believe that Sterling possessed adequate substantiation for Cope's tension relief claims (John Tr. 5569). He also did not believe that Sterling possessed adequate substantiation for the proposition that methapyrilene fumarate at the dosage level contained in Cope had tension-relieving properties (John, Tr. 5569–70). By "adequate substantiation" for tension relief claims for Cope (and methapyrilene fumarate), Dr. John meant one, but preferably two, clinical trials (John, Tr. 5571). This standard he believed was widely recognized by the pharmaceutical industry, including Sterling, which recognized a hierarchy of evidence: well-controlled clinical tests of the drug was most desirable; reports in the scientific literature regarding studies of ingredients in the drug or, at least, similar combinations was the next most preferred, and references in recognized medical texts was the least preferred (John, Tr. 5508). Dr. Robert John also did not believe the substantiation for Cope's tension relief claims would meet the standards he believed would be eventually adopted by the FDA for OTC drugs (John, Tr. 5511).

934. In 1975, the FDA Sedative Panel did not believe that any over-the-counter drugs including methapyrilene fumarate were effective as daytime sedatives for relieving simple nervous tension (Rickels, Tr. 7989, 7996, 8001; CX 465A, p. Z005). The Panel believed that no significant drug-placebo difference could be demonstrated for the over-the-counter drugs tested. The Panel also concluded that some antihistamines (including methapyrilene fumarate) might be effective as nighttime sleep-aids by producing drowsiness and sleep. This same effect, [228] however, constituted a risk in daytime use in ambulatory patients whose activities require mental alertness and coordination (CX 465A, p. Z002). Further, the Panel also doubted whether antihistamines produce any antianxiety effects separable from the production of drowsiness (*Id.*). Additionally, no studies had been given to the Panel demonstrating efficacy of any over-the-counter daytime sedative, including Cope (Rickels, Tr. 8001). For these reasons, a minority of the Panel believed that all over-the-counter daytime sedatives, including those containing methapyrilene fumarate, should be taken off the market (Rickels, Tr. 7989; CX 465A, p. Z003). The majority, however, voted to place these drugs in Category III, that

is, to allow manufacturers a limited time to develop studies to show the efficacy of their drugs (Rickels, Tr. 7989, 7996; CX 465A, p. Z002). However, no research was forthcoming showing efficacy of any over-the-counter daytime sedatives (Rickels, Tr. 7993, 7996). In contrast, the Panel had considered Dr. Rickels' daytime sedative study which compared Compoz, librium, placebo and aspirin. That study concluded that Compoz (a drug which contained 25 mg of antihistamine) was not effective as a daytime sedative for tension relief (Rickels, Tr. 7943–57). Dr. Rickels testified that the members of the Sedative Panel now believe that methapyrilene fumarate should be placed in Category II as not generally recognized as safe or efficacious (Rickels, Tr. 7993).

935. The Food and Drug Commissioner published his Tentative Final Orders in the Federal Register regarding over-the-counter daytime sedatives. That order, 71 C.F.R. 310 (marked as CX 465B, for identification) states that no over-the-counter daytime sedatives can stay on the market beyond December 24, 1979. The order, largely adopting the findings of the Daytime Sedative Panel, in substance gave as its basis that (1) populations may not exist that have symptoms which such drugs combat; (2) antihistamines produce drowsiness (a gratuitious, deleterious side effect) not also associated with antianxiety or antitension properties; and (3) these kinds of drugs may endanger persons taking them instead of helping them (Rickels, Tr. 8180).

936. Sterling relied on two Cope clinicals (RX 236 and RX 237), various articles by Friedman and associates (CX 431), and seven miscellaneous studies in the literature as well as the testimony of Dr. George Goldstein and Dr. Stephen Carson as the basis for its claim that Cope had tension-relieving properties. Sterling also offered into evidence a 1978 study by Sunshine. The Friedman articles are as follows:

Friedman, Arnold P. von Storck, Theordore J. D. and Merritt, H. Houston; *Migraine and Tension Headaches* Neurology; October, 1954, Volume 4, Number 10. [**229**]

Friedman, Arnold P. and Merritt, H. Houston; *Treatment of Headache;* The Journal of the American Medical Association; March 30, 1975, Volume 163.

Friedman, Arnold P.; *Studies in the Pharmacotherapy of Headache;* Neurology; March, 1963, Volume 13, Number 3, Part 2.

Friedman, Arnold, P.; *Treatment of Headache;* Journal of Occupational Medicine; June, 1960.

Friedman, Arnold P.; *Newer Drugs in the Treatment of Headache;* The

Medical Clinics of North America; March, 1964, Volume 48, Number 2.
Friedman, Arnold P.; *What to Do About Headaches;* U.S. News and World Report; October 26, 1964.
Friedman, Arnold P.; *How to Prevent Tension Headache;* Consultant, January 21, 1973, Volume 7.
Friedman, Arnold P. and Elkind, Arthur H.; *Review of Headache,* Part 1; New York State Journal of Medicine, January 15, 1967.
Friedman, Arnold P., Dexter, James and Elkind, Arthur H.; *Chronic Recurrent Headache;* American Medical Association Meeting, June 16–20, 1968,
Friedman, *Studies on Vascular Headaches;* Southern Medical Journal (1957).
Friedman, Arnold, *Studies on Vascular Headaches;* Southern Medical Journal (1953).

The eight miscellaneous articles and the 1978 Sunshine article are as follows: (1) Straus, "Hypnotic Effects of Antihistamine Methapyrilene Hydrochloride" (1955); (2) Noell, "EEG Evaluations of the Sedative Effects of the Antihistamine Drugs" (1955); (3) Feinblatt, "Sedative and Somnifacient Effects of Methapyrilene as Niacinate: Comparison With Methapyrilene Hydrochloride" (1963); (4) Shapiro, "The Use of Methapyrilene Hydrochloride As a Sedative in Somnifacient Agent" (1956); (5) Stern, "Sleep-Inducing Properties of a Non-Barbiturate Analgesic Sedative Preparation in Elderly Patients" (1972); (6) Feinblatt, "New Tranquilizing Soporific for Insomnia" (1958); (7) Sunshine, "A Compositive Study of Excedrin P.M. and Placebo" (1974); and (3) Sunshine, "Hypnotic Activity of Diphenhydramine, Methapyrilene, and Placebo" (1978). With the exception of the 1978 Sunshine study, all these articles were available in the literature while Robert John was medical director at Glenbrook.

937. Neither RX 236, "Clinical Evaluation of Tenquel" nor RX 237, "Clinical Investigation of Tenquel in Human Volunteers" which both compared Tenquel (Cope) with placebos, provide reasonable scientific evidence to support a claim that Cope has **[230]** tension-relieving properties. The methodological flaws in the design of both studies make them unsuitable support for tension relief claims.

938. Although the data and conclusions of RX 236 cannot be properly analyzed because the study lacks a well-defined protocol (Rickels, Tr. 8006), the report does provide a one-page statement regarding the study. That statement makes it clear that the study was not designed to test the effect of Cope on headache alone, nervous tension alone, or both together (Rickels, Tr. 8006). The study did not separate out subjects who had tension from those who had pain. Instead, all test

subjects were to enter information regarding headaches, nervous tension, depression, and generalized aches or pains (Rickels, Tr. 8006; RX 236D). Table 2 (RX 2360) indicates that of the test subjects taking Cope, 731 or 81.8% had headaches; Table 8 RX 236U) indicates 311 or 34.8% had muscular aches and pains, and Table 4 (RX 236Q) indicates 373 (41.7%) had nervous tension. Accordingly, these tables indicate that most test subjects, regardless of their other symptoms, virtually always had pain (Rickels, Tr. 8006). By not separating out subjects who had tension from those who had pain, the data can be cited only for the conclusion that Tenquel (Cope) has an analgesic effect compared with a placebo (Rickels, Tr. 8007). This data cannot provide support that the product provides tension relief. The analgesic effect of the medication which produced pain relief to many test subjects also may have produced a decrease in tension in a limited number of patients by relieving the pain causing the nervous tension. That kind of result does not provide support that a product provides tension relief (Rickels, Tr. 8007). Additionally, the study did not provide for a nurse investigator (Carson, Tr. 16036), so patients were required to self-diagnose their symptoms (Carson, Tr. 16037–38; RX 236D). The instructions accompanying each of the questionnaires allowed the test subjects to take a tablet for headache, nervous tension, depression, and general aches and pains, either alone or in any combination (Carson, Tr. 1600–31, 16034). The study, however, nowhere defines nervous tension or depression, despite the fact these terms can have a wide range of meanings (Rickels, Tr. 8007). If the test subjects misdiagnosed their symptoms, then the data reported could change, thus affecting the test's conclusions (Carson, Tr. 16037–38).

939. Many of the methodological defects of RX 236 are present in RX 237. In particular, the study lacked a well-defined protocol (Rickels, Tr. 8011); the design of the questionnaire is similar to the defective questionnaire used in RX 236 in allowing subjects to take a tablet for tension accompanied or caused by pain; and the study nowhere defines "nervous tension" to aid patients in their unsupervised self-diagnosis (Rickels, Tr. 8011). The data in RX 237, like the data in RX 236, shows almost all the test subjects had headache [231] or generalized aches or pain (Rickels, Tr. 8012; RX 237, pp. Z016, Z019). This kind of data only provides support that Tenquel (Cope) has an analgesic effect compared with a placebo, and, like RX 236, does not provide support that the product provides tension relief (Rickels, Tr. 8011–12).

940. Dr. Tainter stated that he relied on the works of Arnold Friedman for the principle that sedative ingredients can reduce the resistance to analgesics that nervous tension can cause (Tainter, RX 284X). Sterling included methapyrilene fumarate as the sedative ingredient in Cope (Tainter, RX 284Y; RX 284, p. Z001). However, none of Fried-

man's articles provide any reasonable scientific evidence to support the assertion that Cope has tension-relieving properties. None of these articles refer to any clinical test involving the product Cope or any product containing methapyrilene fumarate (Rickels, Tr. 8015). Instead, the articles consist of summary discussions by the author, a well-known expert in the area of headaches (not psychopharmacology) based on his long-term experience working with drugs (Rickels, Tr. 8014). Sterling was aware that Dr. Friedman's articles were based on his experience rather than on clinicals and, in fact, emphasized this point through Dr. G. Goldstein as he identified the various Friedman articles (G. Goldstein, Tr. 15496, 15498, 15500). Additionally, Dr. Tainter acknowledged that Friedman's studies involved barbiturates combined with aspirin and caffeine (Tainter, RX 284Y). Dr. G. Goldstein said that the implication of the Friedman articles was that an ingredient with sedative-like properties was appropriate as an ingredient to treat the tension associated with headaches (G. Goldstein, Tr. 15508). Dr. Tainter felt research in the areas of sedatives offered a reasonable basis for such a conclusion (Tainter, RX 284Y). However, as Dr. Rickels testified, it would not be proper to draw any conclusion about the pharmacological action of methapyrilene fumarate, an antihistamine, either alone or in combination with other OTC products, from information and data on the pharmacological action of a drug containing a barbiturate. While barbiturates and antihistamines both can produce drowsiness or sedation in varying degrees, antihistamines, unlike barbiturates, have not been shown to possess even mild antianxiety properties (Rickels, Tr. 8016).

941. In 1973, Dr. John forwarded to Dancer-Fitzgerald-Sample, Inc. a list of four articles by Friedman and his associates relating to tension and headaches (John, Tr. 5524–26; CX 438). These articles included the following: (1) Friedman, A. P., "Treatment of Headache," *J. Occup. Med.,* 2:268–274, 1960; (2) Friedman, A. P., "How to Prevent Tension Headache," *Consultant,* pp. 16–19, Jan. 1967; (3) Friedman, A. P., "Studies in the Pharmacotherapy of Headache," *Neurology,* 13:27–33, 1968; (4) "Newer Drugs In the Treatment of Headache" (1964). Dr. John had read these four articles before forwarding the list and knew that these articles did not include reports on clinical tests **[232]** either involving Cope or the ingredients at the dosage level found in Cope (John, Tr. 5525–26). The fourth article on the list, "Newer Drugs in the Treatment of Headache" (1964) sets forth Friedman's opinion that aspirin and tranquilizers alone may not be as effective in treating headache as an analgesic-sedative/tranquilizer combination. The drugs cited in the article for examples of such combinations all were barbiturates (Robert John, Tr. 5529–30). At that

time, Dr. John knew that antihistamines did not belong to the barbiturate class (John, Tr. 5531).

942. The eight miscellaneous studies referred to earlier (Noell, T. Feinblatt, H. Feinblatt, Straus, Shapiro, Stern, and Sunshine '74 and '78) do not provide reasonable scientific evidence to conclude that methapyrilene fumarate, an antihistamine, has tension-relieving properties. Dr. George Goldstein agreed that these eight studies were designed to test and made conclusions regarding the sleep-inducing properties of either methaprilene fumarate or methapyrilene hydrochloride (Rickels, Tr. 8163–67; G. Goldstein, Tr. 15750–53). A study designed to detect sleep-inducing properties of a drug is different from a study designed to test tension or anxiety-relieving properties of a drug (Rickels, Tr. 8183). A sleep study is designed to test whether a drug provides a specific benefit, *i.e.*, bringing relief to a person who has difficulty following asleep or staying asleep. That issue is different from the issue of whether a drug provides relief from tension, stress, or anxiety (CX 465A, p. Z002). No conclusion about tension relieving effects of a drug can be drawn from the sedative effects of a drug, for not all sedatives have tension-relieving properties (Rickels, Tr. 8016). Consequently, these eight miscellaneous studies only support a claim that methapyrilene may have sleep-inducing properties.

943. Dr. Goldstein agreed that the test subjects in the eight sleep studies who took any of the various dosage levels of methapyrilene probably experienced decreased sensory perception, an inability to react to the environment, and reduction in alertness beyond a safe level (G. Goldstein, Tr. 15753). He also agreed with the FDA OTC Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products Panel that a daytime sedative (as opposed to a nighttime sleep-aid) should not have these unsafe effects (G. Goldstein, Tr. 15743). He believed that any drowsiness effect of the methapyrilene fumarate in Cope would be counteracted by the ingredient of caffeine (G. Goldstein, Tr. 15745). He cited no evidence for this belief in contradiction to his belief, as of 1972, Cope (which *includes* caffeine) contained a warning label that "This preparation may cause drowsiness. Don't drive a car or operate machinery while taking this medication" (G. Goldstein, Tr. 15749).

944. In addition to the material listed in F. 936, *supra,* the record also includes three excerpts from journals, some **[233]** bibliographic materials, some technical data, and letters from doctors regarding the Cope formula as the basis for its claim that Cope had tension-relieving properties. The journal excerpts include: (1) Blumenthal "Chronic Headache, An Analysis of 1,254 Cases Observed for More Than Six Months With Suggestions Regarding Their Diagnosis and Treatment" (1957); Lederer, "Otorhinolaryngologic Aspects of Headache

and Head Pains" (1971); and Caviness, V., "Current Concepts - Headache" (1980). The bibliographic material includes: (1) RX 232, "Review and Bibliography of the Ingredients of Cope, An New Analgesic Formulation for Women"; (2) RX 240, "Methapyrilene Bibliography," (3) RX 242N, bibliographic references from a Monsanto Lab report submitted to the FTC; and (4) RX 233, "Cope: Tension Headache Background." The technical data includes: (1) RX 241, "Methapyrilene Hydrochloride and Methapyrilene Fumarate," and (2) RX–411, "Technical Information on Methapyrilene." The letters from the doctors (RX 235) were written by Dr. Batterman, Dr. Bird, W.P. Blackmore, Dr. Harris, Dr. Sadone, and Dr. Cass.

945. As to the three journal excerpts, the authors of each of the articles states that the combination of a sedative or a tranquilizer produces the most effective relief for tension headaches (G. Goldstein, Tr. 15411–12; 15435–36; 15446–48). These articles are no basis to conclude methapyrilene fumarate can relieve tension.

946. The bibliographic material cited by respondent provides support only for claims regarding sedative or hypnotic effects of methapyrilene. RX 232, "Review and Bibliography on the Ingredients of Cope, A New Analgesic Formulation For Women," cites only the Shapiro and Straus articles (CPF 1012, 1016) for support of the claim that 8.5 mg of methapyrilene fumarate is a subhypnotic dose of Cope which will "provide relaxation from tension and strain without producing drowsiness" (RX 232 p. O). Neither of these articles make any conclusions whether 8.5 mg of methapyrilene can provide relaxation from tension and strain. Instead, both studies were designed and made conclusions regarding the *hypnotic* effects of methapyrilene. In addition, the Shapiro study made conclusions regarding methapyrilene's effect on hyperactivity in children 4 weeks to 12 years of age (RX 232, p. O; RX 250–Shapiro). RX 240, "Methapyrilene Bibliography," makes numerous references to the sedative and hypnotic effects of methapyrilene, particularly the effect of drowsiness (RX 240 A, B, E, G, K, L, Q, S. T, U, and W). However, the record is silent about whether any references cited in this bibliography report any conclusions regarding antitension or antianxiety effects of methapyrilene. RX 242N, the bibliographic section of a document submitted by Monsanto to the FDA in September of 1972 contains a list of ten articles under the heading, "Hypnotic and Sedative Action" (RX 242N). Respondent cites this document only as "a bibliography of authorities demonstrating the *sedative* properties of methapyrilene" (G. Goldstein, Tr. 15460). **[234]**

947. Neither the materials offered by Sterling nor the testimony of its witnesses, Dr. Steven Carson and Dr. George Goldstein, are sufficient to substantiate the claim that Cope had tension-relieving prop-

erties. The two studies comparing Tenquel (Cope) with a placebo, RX 236 and RX 237, both had methodological flaws so that these studies only measured the analgesic effect of Cope. Further, both clinicals were signed by Dr. Carson (Rickels, Tr. 8004, 8010) who maintained that he was not involved in their design. The literature reporting tests of various dosages of methapyrilene hydrocholoride and methapyrilene fumarate provide no basis for claims Cope has tension-relieving properties, since each of these studies was designed as a sleep study and not a tension relief study. The Friedman literature largely consisted of reports based on Friedman's extensive treatment of patients in pain as well as his familiarity with the area of headache treatment. Further, these articles did not report any well-controlled clinical study testing the tension-relieving property of Cope or products containing the ingredients in Cope. His recommendation that barbiturates and analgesics are most effective in treating headaches associated with tension provides no rationale for Cope's Formula, since methapyrilene fumarate is not a barbiturate. To the extent that Dr. George Goldstein relied on it for his opinion that Cope had tension-relieving qualities on the above literature, his opinion is flawed. Further, because of his limited expertise in pharmacology generally and in clinical testing of tension relief specifically (G. Goldstein, Tr. 14746–48, 14753–54), his opinion regarding the tension-relieving properties of Cope does not carry much weight on the question whether Cope had tension-relieving properties. Finally, Dr. Goldstein was not employed at Sterling until 1975 so his opinion could not have been relied upon by Sterling as a reasonable basis for its claims. Cope's claims were disseminated 1969 through 1971.

947A. The inadequacy of Sterling's sources is further confirmed by the action of the FDA Sedative Panel and the Commissioner's Tentative Final Orders that methapyrilene belongs in Category II, that is, drugs which lack evidence of being either safe or efficacious as a daytime sedative for tension relief. Finally, it was the testimony of Dr. Rickels, one of the country's foremost experts in psychopharmacology, that the available scientific evidence does not support any tension-relieving claims for the combination of ingredients at the dosage level found in Cope. Thus, as alleged in Paragraph 16 of the Complaint, during the time respondent disseminated tension relief claims for Cope, as alleged in Paragraph 15 of the Complaint, there was no reasonable basis for that claim on the basis that Cope contained methapyrilene furmarate. **[235]**

H. *The Ingredients in Midol, Either Individually or in Combination, Do Not Relieve Depression*

1. Introduction

948. Depression is a term with a wide range of meanings (Rickels, Tr. 8007). The symptoms include feelings of being "blue," hopeless, and uninterested in one's activities or life (Rickels, Tr. 7959).

949. Depression can be appropriately treated by nondrug methods such as psychotherapy or psychiatric counseling. It also can be appropriately treated with antidepressant drugs (Rickels, Tr. 7910–11).

950. From December of 1966 up to November of 1973, Sterling made claims in advertisements that a recommended dose of Midol relieves depression and improves the user's mood (CX 634; F. 390–394, *supra*).

951. The ingredients in Midol are aspirin, caffeine, and cinnemadrine hydrochloride. None of these ingredients improve the user's mood (Rickels, Tr. 8021). In fact, caffeine may be contraindicated as a mood-brightener because of its possible effect of heightening awareness of pain.

952. The recommended dosage of Midol contains 64 mg of caffeine (G. Goldstein, Tr. 15575). Caffeine serves two functions in Midol: (1) a stimulant to the central nervous system and (2) a mild diuretic (G. Goldstein, Tr. 15095, 15577). These functions of caffeine are said to give Midol an antidepressant effect (Fields, Tr. 16772).

953. As a stimulant, Sterling contends that a therapeutic oral dose of caffeine can produce such effects as increased mental alacrity, more acute and discriminating sensations, facilitation of asociation of ideas, and retardation of actions owing to more discriminating judgment (G. Goldstein, Tr. 15578, 15591–92). Sterling's position is that caffeine also produces "brighter spirits" (G. Goldstein, Tr. 15578). As a diuretic, Sterling contends that the caffeine in Midol will have a direct effect on mood by relieving edema including the pressure of water on the brain (G. Goldstein, Tr. 15094, 15602; Fields, Tr. 16773).

954. The recommended dose of Midol contains 455 mg of aspirin. The primary role of aspirin in Midol is as an analgesic (Hartman, Tr. 9437). Aspirin does not have any antidepression properties (CX 466, p. 35355). Respondent's witness, Dr. George Goldstein, agreed that aspirin's role in Midol was for pain relief and that aspirin has no direct effect on mood. Any effect on mood would be caused solely by aspirin's ability to relieve pain (G. Goldstein, Tr. 15549). He further testified that on the basis of available evidence, Sterling **[236]** could not make claims that aspirin affects mood (G. Goldstein, Tr. 15559). Further, he agreed that the evidence available regarding the tryptophan effect of aspirin was insufficient to make any judgment about aspirin's effect on mood (G. Goldstein, Tr. 15561).

955. Midol contains cinnamedrine hydrochloride (RX 228). Cinnamedrine hydrochloride functions as a uterine antispasmodic to relieve muscle cramps (Hartman, Tr. 9137; Rickels, Tr. 8019; RX 228). This ingredient, either by itself or with other OTC ingredients, has no effect as a mood brightener (Rickels, Tr. 8022). Dr. Goldstein agreed that cinnamedrine hydrochloride has no direct effect on mood (G. Goldstein, Tr. 15549).

956. Sterling relied for its claim that the ingredients in Midol have depression relieving properties on (1) the testimony of Dr. George Goldstein, Dr. Fields and Richard Hartman as well as (2) two medical texts (Krantz, J. *The Pharmacologic Principles of Medical Practices,* "Central Nervous System Stimulants" (1958) and Dalton, K., "The Premenstrual Syndrome" 1964; (3) a compendium, "The Dispensatory"; and (4) a report by Bellet, "The Effect of Caffeine Ingestion on Catecholamine Release" (1969). Additionally, Sterling relied on an internal memorandum reciting the caffeine amounts in various beverages (RX 227). Sterling also submitted in 1972 a two-page document (RX 28) to the Internal Analgesic Panel and the Miscellaneous Internal Products Panel which discussed the rationale for the ingredients in Midol. Sterling did not introduce nor cite any clinical studies indicating that increased "brighter spirits" have been measured at 64 mg of caffeine, the recommended dosage level of Midol (G. Goldstein, Tr. 15590).

2. Caffeine Does Not Have Depression-Relieving Properties

957. According to Sterling, nervous tension, stress, irritability, fatigue, and depression are symptoms that are associated with the menstrual syndrome (Hartman, Tr. 9166–97). The expression "menstrual syndrome" encompasses the whole range of symptoms that accompany menstruation (Hartman, Tr. 9136). The caffeine in Midol is supposed to relieve the depression, fatigue, and irritability associated with the menstrual cycle (G. Goldstein, Tr. 15094, 15096). Dr. Goldstein admitted that "depression" did not refer to the psychiatric term but rather to a feeling of being "down" or "depressed" as a result of being in pain (G. Goldstein, Tr. 15096, 15100, 15113, 15114, 15116). Caffeine's action as a stimulant was supposed to act to ameliorate that kind of mood because a therapeutic dose of caffeine could produce "brighter spirits" (L. Goldstein, Tr. 15096, 15578). Dr. Goldstein relied on Krantz, "Central Nervous System Stimulants" for this proposition (G. Goldstein, Tr. 15102, 15578). However, no clinical evidence of any kind testing caffeine in humans suffering from depression was referred to by Dr. Goldstein. **[237]**

958. Dr. Goldstein admitted that caffeine's effect on mood was not a psychotropic effect (G. Goldstein, Tr. 15096). Relying on Bellet,

"Effects of Coffee Ingestion on Catecholamine Release" (1969), Dr. Goldstein explained that the ingestion of caffeine stimulates the release of catecholamines from storage depots in the body. The catecholamines, in turn, increase the heart rate and cause an increase in mental alertness and brightens mood (G. Goldstein, Tr. 15111–12). However, no clinical evidence of any kind testing caffeine as a "mood brightener" by affecting the catechomaline release in humans suffering from depression was referred to by Dr. Goldstein.

959. Dr. Goldstein testified that caffeine would have the same effect as a "mood brightener" even in the absence of pain but that when a person starts off from the experience of pain, caffeine's action is perceptible in different ways (G. Goldstein, Tr. 15117). However, in contradiction of Dr. Goldstein's statement, Dr. Tainter, Sterling's Director of Research and the founding member of the SWRI, stated caffeine's action as a stimulant may cause a person in pain to feel the pain even more intensely (Tainter, CX 417B). Dr. Tainter expressed this opinion in an internal communication discussing the effects of caffeine in various analgesics. He concluded that caffeine's action on the central nervous system would tend to diminish the analgesic effectiveness of compounds (CX 417B).

960. It is the aspirin ingredient in Midol which reduces the pain, not the caffeine. Indeed, the caffeine may enhance pain. However, Midol can not be characterized as an antidepressant because of its analgesic action for the same reasons aspirin could not be characterized as an antianxiety agent because it relieved the pain causing (or aggravating) the tension.

961. In 1972, Sterling submitted a 2–page document (RX 228) to the FDA OTC Internal Analgesic Panel and the Miscellaneous Internal Products Panel that offered Sterling's rationale for the ingredients in Midol (G. Goldstein, Tr. 15096). Neither this document nor any other document relating to Midol was ever submitted to the FDA OTC Nighttime Sleep-Aid, Daytime, Sedative, and Stimulant Products Panel, which considered products asserted useful as tension relievers and/or mood elevators (Rickels, Tr. 8018; G. Goldstein, Tr. 15603). The document, RX 228, defines the purpose for which Midol is marketed. It states: "The rationale for this product, promoted primarily for relief of dysmenorrhea, is the provision of the analgesic activity of aspirin and caffeine, and the adjunctive papaverine-like uterine spasmolytic action of cinnamyl ephedrine" (RX 228). "Dysmenorrhea" is a broad term for menstrual pain. The document nowhere mentions that Midol generally or caffeine specifically affects mood by relieving edema through diuresis (G. Goldstein, Tr. 15602). That document also does not make any mention about caffeine's effect as a "mood brightener." [238]

962. L. S. Goodman and A. T. Gilman whom Dr. Goldstein characterized as "among the leading lights of American pharmacology" and "probably the single greatest authority on pharmacology in this country" (G. Goldstein, Tr. 15590) did not list "brighter spirits" in their list of the effects of a therapeutic dose of caffeine found in their text, *The Pharmacological Basis of Therapeutics* (G. Goldstein, Tr. 15593–94). The Goodman and Gilman list includes the following: "psychic and sensory functions," "clearer flow of thought," "delays drowsiness," "capable of more sustained intellectual effort" and "more perfect association of ideas" (G. Goldstein, Tr. 15593–94). Dr. Goldstein argued that the Goodman and Gilman list, with the exception of their omission or "brighter spirits," was very similar to Dr. Krantz's list of the effects of a therapeutic dose of caffeine (G. Goldstein, Tr. 15592). He argued that the Goodman and Gilman list was compatible with the term "brighter spirits" (G. Goldstein, Tr. 15594). However, this list cannot be characterized as compatible with "brighter spirits" since, as Dr. Goldstein agreed, a more perfect association of ideas could, in fact, be a "curse" rather than a mood brightener depending on what a person was thinking, as well as "whole host of variables" (G. Goldstein, Tr. 15594–95).

963. Sterling was aware that not all accepted texts in pharmacology listed "brighter moods" as an effect of a therapeutic dose of caffeine. The Goodman and Gilman list, which did not, was among the various documents included in RX 221 which were stamped "M. L. Tainter, M.D." (G. Goldstein, Tr. 15591).

964. Beyond the question of level of agreement about the effects of caffeine, the scientific community is undecided as to what *amount* of caffeine constitutes a therapeutic dosage of caffeine which will produce *any* of the effects listed by Krantz and Goodman and Gilman. Cope contains 64 mg of caffeine. Dr. Goldstein admitted, "There is a clear divergence of opinion" (G. Goldstein, Tr. 15593). He thought 50–150 mg of caffeine was the amount in an average cup of coffee and that this range constituted a therapeutic dose (G. Goldstein, Tr. 15583). An internal Sterling memo to Dr. Tainter stated coffee contained 90–120 mg of caffeine (RX 227). Goodman and Gilman defined a therapeutic dose of caffeine as between 150–250 mg for an adult (G. Goldstein, Tr. 15592). Dr. Krantz stated that an average cup of coffee contains a therapeutic dose of caffeine which ranged between 50–100 mg (G. Goldstein, Tr. 15588). However, elsewhere Dr. Krantz states that 200 mg is necessary for caffeine to act as a stimulant (G. Goldstein, Tr. 15587). Dr. Rickels' opinion was that caffeine acted as a stimulant at dosages 100–200 mg, the equivalent of one and a half cups of coffee (Rickels, Tr. 7974). The FDA Nighttime Sleep-Aid, Daytime Sedative, and Stimulant Products Panel concluded that a thera-

peutic dose of caffeine which would act as a stimulant to produce alertness and to counter fatigue was 100–200 mg (CX 465, p. Z008). Dr. Goldstein admitted that the dosage level of [**239**] caffeine needed to produce the effect of "brighter spirits" is extremely variable, depending on individual physiology, metabolism, biochemistry, and "a whole host of factors" (G. Goldstein, Tr. 15581–83). Dr. Goldstein acknowledged that, in fact, "brighter spirits" may not result from the ingestion of caffeine, even when consumed in amounts larger than what he would characterize as a therapeutic dose, *i.e.*, an average cup of coffee (G. Goldstein, Tr. 15583–84).

965. Dr. Fields referred in his testimony to a study by Dr. A. Goldstein which was discussed by the FDA Internal Anaglesic, Antipyretic and Antirheumatic Products Panel regarding a positive association between the mood elevating effect of caffeine and sensitivity to wakefulness caused by caffeine (Fields, Tr. 16768–69; CX 446, p. 35483). However, Fields acknowledged that the lowest dosage level of caffeine tested was 150 mg. The only other dosage level tested was 300 mg (Fields, Tr. 16771). The recommended dosage of Midol, however, contains 64 mg of caffeine.

966. Dr. Goldstein stated that the two different pharmacologic actions of caffeine, stimulation and diuresis, were not attributable to a similar dose range (G. Goldstein, Tr. 15600). There is no evidence in the record whether the 65 mg of caffeine in Midol is sufficient to relieve edema by diruesis in any significant population.

967. Dr. Fields was not prepared to state that the caffeine in the recommended dosage of Midol produced a diuretic effect which would affect mood (Fields, Tr. 16773). Instead, he said that caffeine in the amount in Midol was sufficient to affect mood because of the cumulative effect of caffeine as a diuretic and a stimulant (Fields, Tr. 16773). He admitted he could not state the amount of caffeine in Midol which produced a sufficient diuresis and the amount in Midol which produced the stimulant effect since the effect on mood was a "cumulative physiological response" (Fields, Tr. 16773). He gave no evidence of any kind in support of this proposition.

968. Richard Hartman, respondent's witness, stated that one of the sources for associating the symptoms of tension, irritability, depression, and fatigue with the "menstrual syndrome" is a text by Katherine Dalton, "The Premenstrual Syndrome" (1964) (Hartman, Tr. 9166–67, 9186). He also said he relied on various articles in consumer magazines and medical articles (Hartman, Tr. 9136). However, he could not identify any of these other sources (Hartman, Tr. 9187). Sterling's theory as to the causes of the psychological symptoms of moodiness and irritability (*i.e.*, the "menstrual syndrome") differs from Dr. Dalton's explanation. In her subsequent text, "The Premen-

strual Cycle," Dr. Dalton states that the psychological symptoms of tension, irritability, depression, and lethargy (*i.e.*, the "menstrual syndrome") appear to be due to a hormonal imbalance in the production of progesterone and **[240]** corticosteroids. This imbalance causes, among other things, water retention, sodium retention, potassium depletion, and alterations of the bloods sugar level (Hartman, Tr. 9196–98). Hartman admits he had never discussed with anyone at Sterling whether or not the psychological symptoms of the menstrual cycle are attributable to hormone imbalance or sodium retention, or potassium depletion (Hartman, Tr. 9197, 9199), nor did he ever suggest that the ingredients in Midol affected the hormonal imbalance that Dr. Dalton states causes the "menstrual syndrome." Instead, he had always discussed the symptoms involved in the "menstrual syndrome" as related to head or back pains present during the menstrual cycle (Hartman, Tr. 9168, 9199).

969. Dr. G. Goldstein did discuss moodiness, including irritability, as caused by edema or water retention, a factor discussed by Dr. Dalton (G. Goldstein, Tr. 15094). However, he knew of no studies that showed Midol influenced potassium, sodium, progesterone, or corticosteroid levels in human subjects, the factors Dr. Dalton described as causing the water retention in the first place (G. Goldstein, Tr. 15605).

970. The testimony of Dr. George Goldstein, Richard Hartman, and Dr. Fields is not sufficient to substantiate the claim that Midol has antidepressant properties because the documents on which they base their opinions do not substantiate these opinions. RX 228, a Sterling submission to the FDA, characterized Midol as a drug primarily providing analgesic activity associated with menstruation (F. 961, *supra*). Dr. George Goldstein and Richard Hartman also characterized Midol as a drug for pain relief whose effect on mood simply was a by-product of reducing or eliminating head and back pain. This is not unlike the effect of aspirin on tension that occurs after it relieves a headache. The evidence discussed by Dr. Goldstein and Dr. Fields revealed that substantial controversy exists in the scientific community with regard to the amount of caffeine which constitutes a therapeutic dose which would act as a stimulant. It is by no means accepted that 64 mg, the amount of caffeine is the recommended dosage of Midol, is a therapeutic dose for any purpose. No studies involving human subjects have shown that 65 mg of caffeine acted as "mood brightener" either because of caffeine's effect as a diuretic or stimulant or as a result of the cumulative effect of caffeine as a diuretic and a stimulant. Finally, the possibility exists, raised by respondent's past medical adviser, Dr. Tainter, that caffeine can never act as a "mood brightener" because it may act as a pain height-

ener. Thus, as alleged in Paragraph 16 of the Complaint, during the time respondent disseminated anti-depressant or mood elevating claims for Midol, as alleged in Paragraph 15 of the Complaint, there was no reasonable basis for such claims. Furthermore, as alleged in Paragraph 27 of the Complaint, the analgesic ingredient referred to in advertisements for Midol is nothing other than ordinary aspirin and the [241] stimulant in Midol is caffeine. Thus implied claims in advertisements to the contrary, as alleged in Paragraph 26 of the Complaint, are false.

I. *Friedman Studies Do Not Show Cope Is A More Effective Treatment For Nervous Tension Headaches Than Any Other OTC Analgesic*

971. Sterling supplied a list of ten articles by Arnold Friedman (CX 431) in response to a 1973 subpoena asking for the studies referred to in the Cope advertisements claiming Cope's superiority over other OTC analgesics for the treatment of nervous tension headaches. Those advertisements stated:

> Important studies made at the world's leading headache clinic show that for relief of severe nervous tension headaches a combination of a pain reliever and a sedative provides greater relief than either medication alone. Of all the leading remedies you can buy for ordinary nervous tension headaches, only Cope combines a gentler relaxer with a powerful pain reliever for really effective relief (CX 272, 283, 287; CPF 292–93).

These 10 articles are listed in F. 936.

972. According to Dr. Tainter, Director of Research for Sterling from 1943–1969, Cope's formula was designed to be particularly appropriate for the treatment of nervous tension headache (Tainter, RX 284X, 284Y). The formula included both aspirin and methapyrilene fumarate, based on the theory that a sedative ingredient and an analgesic would be the most effective combination for the treatment of nervous tension headache (Tainter, RX 284X, 284Y; G. Goldstein, Tr. 15489). Dr. Tainter stated that the studies of Dr. Arnold Friedman were the basis for Cope's formula (RX 284X, 284Y). However, as Dr. Tainter was well aware, none of Friedman's articles either involved Cope or any products containing the ingredients at the dosage levels found in Cope (Rickels, Tr. 8015; Tainter, RX 284Y). In fact, Dr. Tainter acknowledged that the Friedman studies involved a barbiturate combined with aspirin and caffeine (RX 284Y). Cope, however, contains, in addition to aspirin, an antihistamine (methapyrilene fumarate) and caffeine. It would not be proper to draw any conclusion about the pharmacological action of methapyrilene fumarate, an antihistamine, either alone or in combination with other OTC products, from information and data on pharmacological action of a drug con-

taining a barbiturate. While barbiturates and antihistamines both can produce drowsiness or sedation in varying degrees, antihistamines, unlike barbiturates, have not been shown to possess even mild antianxiety properties (Rickels, Tr. 8016). [242]

973. Therefore, as alleged in Paragraph 19 of the Complaint, the "tests and studies" referred to in Cope advertisements, do not prove that a recommended dose of Cope is more effective for the relief of "nervous tension headaches" than recommended doses of all other nonprescription analgesics.

J. *The Fact That Vanquish, Cope, and Midol Contain Aspirin Is Not Known To A Substantial Number of Consumers And Is A Material Fact Which Should Be Disclosed In Advertising*

974. Aspirin is known to have a wide range of adverse effects, some of which are serious and even potentially life-threatening. The FDA-OTC Analgesics Panel detailed its findings in this area in its final report (CX 466, at 35383–35411). Among the more serious are the adverse effects on the gastrointestinal tract and on aspirin sensitive individuals. F. 979–1013, *infra.* Vanquish, Cope and Midol each contains aspirin as an active ingredient.

1. Gastrointestinal Distress

975. Ingestion of aspirin results in or is highly associated with adverse reactions in the gastrointestinal tract which range from very slight to very serious effects (Grossman, Tr. 7468; CX 466, p. 35386). These adverse reaction can be divided into two categories, *i.e.,* those that are apparent to the subject who is taking the aspirin and those that can only be detected by investigations conducted on the subject by examination of the lining of the stomach and intestines (Grossman, Tr. 7468–69). Those side effects apparent to the subject include systems broadly classified as dyspepsia (heartburn, pain, and discomfort in the upper stomach), overt and sometimes massive bleeding by vomiting of blood or the passing of blood in the stool caused by diffuse lesions (tissue abnormalities), hemorrhages in the mucosa of the stomach lining, and gastric ulcers (Grossman, Tr. 7468, 7472, 7475, 7484, 7489). Those side effects which are not readily apparent to the subject include occult (unseen) bleeding and microscopic lesions, *i.e.,* damage to the gastric mucosa (Grossman, Tr. 7468, 7470). F. 979–992, *infra.*

976. The nature of the evidence that aspirin results in or is very highly associated with these side effects includes both animal and human studies. The available animal and human studies, as well as a plausible mechanism accounting for the association between aspirin ingestion and the adverse effects of aspirin (F. 979, *infra*), support the

view that aspirin causes or is highly associated with adverse effects (Grossman, Tr. 7643–44).

977. The human studies regarding the adverse effects of dyspepsia, bleeding, and ulcers are not exclusively well-[243]controlled clinicals because of ethical consideration, *i.e.,* the side effects can be disabling and even life-threatening. Accordingly, epidemiological studies, *i.e.,* studies of populations in which the incidence of a disease or conditions in a population is correlated with other facts that occur in that population such as drug ingestion (Grossman, Tr. 7531) and anecdotal evidence become of great importance (Grossman, Tr. 7459, 7656).

978. Sterling, by adding buffers to Cope, Midol, and Vanquish, recognized that aspirin can cause gastric distress. Similarly, Sterling's claim that the manufacturing process used to produce Bayer makes it therapeutically superior to other aspirin also attests to the recognition that aspirin can cause gastric distress. However, neither the addition of these buffers nor the alteration of manufacturing process makes aspirin in any sense risk-free (F. 991, *infra*).

979. While the precise means by which aspirin injures the gastric mucosa, and thus causes adverse effects on the gastrointestinal tract, has not been established, at least two mechanisms are involved. One mechanism is the "topical action" (the Davenport mechanism) by which aspirin acts directly on the stomach lining by being absorbed into and through the lining. Absorption of aspirin into the muscosal cell causes breakdown of the cell barrier which normally protects the stomach lining from its own acid secretions (CX 466, p. 35388). The other mechanism is the "systemic action" by which aspirin affects the gastrointestinal tract after it has been absorbed into the blood and is carried by the blood back to the stomach lining (Grossman, Tr. 7481). The FDA's OTC Internal Analgesic Panel, like Dr. Grossman, believed that there was convincing evidence that the systemic effects of aspirin played a role in aspirin-induced gastrointestinal hemorrhage (CX 466, p. 35386; Grossman, Tr. 7484). However, Dr. Grossman disagreed with the Panel's emphasis on platelet functions as the basis for the systemic mechanism. He felt the better explanation involves aspirin's inhibition of the synthesis of prostaglandins, the necessary protective substances in the gastric mucosa which, when not present, decrease the ability of the lining of the stomach to withstand injurious actions of digestive juices (Grossman, Tr. 7482, 7639).

980. There is also convincing evidence that aspirin particles lodged on gastric mucosa have an erosive effect and cause lesions that can be detected by gastroscopic examination in humans (*e.g.,* Danhof, Tr. 16903–04; Grossman, Tr. 7596–97; CX 466 at 35387–88).

981. Aspirin is almost universally recognized as a cause of dyspepsia (Grossman, Tr. 7471). The estimated incidence of dyspepsia in in-

dividuals who take occasional doses of aspirin on [244] an intermittent basis is up to 10% (Grossman, Tr. 7470, 7682; CX 466, p. 35387). However, the estimated incidence increases to between 10–20% among those who take large doses on a regular basis over longer periods of time (Grossman, Tr. 7470–71). Dyspepsia after aspirin ingestion also occurs more frequently in patients with peptic ulcers, gastritis and duodenitis (CX 466, p. 35387).

982. Dyspepsia as a side effect can vary from a trivial complaint that is not of importance when compared with the headaches, aches, or pain, for which the aspirin was taken, to a major side effect such as gastric ulcer (Grossman, Tr. 7471–72). Some of the less harmful effects of dyspepsia, like heartburn or gastric pain, may nevertheless be more incapacitating to the individual than the headache or aches and pains for which the individual took the aspirin in the first place. In such instances, the side effect of the aspirin (dyspepsia) outweighs any therapeutic effect from the aspirin (Grossman, Tr. 7486). It is possible to avoid such side effects by using alternative therapeutic agents (Grossman, Tr. 7486).

983. All individuals normally lose approximately two to five milliliters of blood daily from the blood vessels in the stomach lining or the gastrointestinal tract (Grossman, Tr. 7478–79; CX 466, p. 35389). Aspirin ingestion can increase this occult bleeding by two or three times (Grossman, Tr. 7479). Usually, such increased bleeding has no clinical importance in that it need not lead to any disabilities nor be associated with any symptoms. No relation between occult bleeding and massive gastrointestinal bleeding or gastric discomfort has been established (Grossman, Tr. 7633–34). In rare instances, however, it can be the direct cause of anemia in persons who, for reasons other than aspirin ingestion, are predisposed to having anemia (Grossman, Tr. 7480; CX 466, p. 35389).

984. Although the cause and effect relationship has not been conclusively established, there exists a high degree of association between aspirin intake and unpredictable, massive bleeding in the gastrointestinal tract (Grossman, Tr. 7722). An association between ingestion of single doses and massive blood loss also have been reported (Grossman, Tr. 7719). Severe gastrointestinal blood loss is the most serious side effect of aspirin on the gastrointestinal tract (CX 466, p. 35391). There is between a 4 to 10% mortality rate from gastrointestinal bleeding (regardless of its cause) which increases rapidly with age so that, at above age 45, a very significant mortality rate is seen (Grossman, Tr. 7424; CX 466, p. 35392). Clinically important gastrointestinal blood loss usually requires medical treatment including blood transfusions and surgery (Grossman, Tr. 7472–73; CX 466, p. 35391). The incidence of massive bleeding due to aspirin ingrestion is not

insignificant (CX 466, p. 35392). Dr. Grossman testified that in his experience, in his patients who have clinically significant bleeding, the **[245]** incidence of associated aspirin ingestion is 20 to 30% (Grossman, Tr. 7473). He also testified that one study indicated that aspirin ingestion was second only to digitalis ingestion as a cause for drug related hospital admissions. Further, he testified that in those admitted because of aspirin ingestion, bleeding from the gastrointestinal tract was a major manifestation (Gross, Tr. 7475; CX 466, p. 35392).

985. There is a recognized higher risk of massive gastrointestinal blood loss in all persons with peptic ulcers (Grossman, Tr. 7485). Peptic ulcers are ulcers which occur in those portions of the gastrointestinal tract which are bathed by the gastric juices (Grossman, Tr. 7469). Approximately 10% of the population will, at some time during their lifetime, have a peptic ulcer. Persons with peptic ulcers should avoid ingestion of aspirin (Grossman, Tr. 7485). Persons who suffer the apparent side effect of dyspepsia also should avoid aspirin ingestion, for some of these persons may have an undiagnosed peptic ulcer, and therefore are in a high risk category for massive gastrointestinal bleeding (Grossman, Tr. 7485).

986. Aspirin may not only present a grave risk to those persons with preexisting peptic ulcers by increasing gastrointestinal bleeding, but in large doses may be the cause of stomach (gastric) ulcers (Grossman, Tr. 7720). There is also a likelihood that regular use of OTC doses of aspirin may contribute to gastric ulcer (Grossman, Tr. 7720–21). A gastric ulcer is a defect in the lining of the stomach which usually takes the form of a loss from half an inch to an inch in diameter of the substance of the tissue that lines the stomach (Grossman, Tr. 7476). Gastric ulcer is a serious disease which can be incapacitating as well as life-threatening (Grossman, Tr. 7478). Each year a few thousand cases of gastric ulcers can be attributed to aspirin ingestion. This amounts to approximately 20% of all cases of gastric ulcers (Grossman, Tr. 7478). By conservative estimate, most notably reported by Levy in his Boston Collaborative Group studies, aspirin ingestion results in 10 out of every 100,000 users developing a gastric ulcer, requiring hospitalization (CX 466, p. 35390). In individuals attending clinics for the treatment of arthritis, rheumatoid arthritis, or osteoarthritis who are being treated with aspirin, the incidence of gastric ulcer is approximately 30% (Grossman, Tr. 7655).

987. In support of the relationship between aspirin and gastric ulcer, Dr. Grossman discussed both the Boston Collaborative Study by M. Levy and also Kenneth Ivey's study, "Incidence of Gastric Lesions in Patients With Rehumatic Diseases." Additionally, respondent's witness, Dr. Danhof, commented on a study entitled "A Randomized Controlled Trial of Aspirin in Persons Recovered from Myocardial

Infarction" (1980) (the NIH Stroke Study) which also provided a further basis for concluding that aspirin causes ulcers. In the Levy study, the [246] author concluded that the epidemological data he collected was consistent with the hypothesis that heavy aspirin use *i.e.,* regular use of aspirin at least four days per week for at least three weeks, may have an association with ulcers (Grossman, Tr. 7645). The Ivey study, which Dr. Grossman characterized as a survey, involved 82 patients with rheumatic disease who were receiving chronic aspirin therapy. The subjects were on doses of aspirin prescribed by their doctors for treatment. Each subject was examined by endoscope. The study concluded that patients taking chronic aspirin therapy for rheumatic diseases have a higher than suspected incidence of gastric ulcer and erosions (Grossman, Tr. 7689). This study, while not conclusive, provides another piece of suggestive evidence that allows the conclusion that aspirin is ulcerogenic (Grossman, Tr. 7717). The NIH Stroke Study, "A Randomized Controlled Trial of Aspirin in Persons Recovered from Myocardial Infarction" (marked for identification as CX 749), was designed to determine whether regular administration of aspirin in individuals who experienced at least one myocardial infarction would result in a significant reduction of mortality over a 3–year period. The side effects of the administration of aspirin were also studied (Danhof, Tr. 17298). The aspirin dosage was three tablets a day, *i.e.,* one gm (Danhof, Tr. 17300). The data showed that twice as many patients in the aspirin groups as the placebo group had symptoms suggestive of peptic ulcer, gastritis, erosion of the stomach mucosa, bloody stools, and symptomatic gout. Three times as many of the aspirin group complained of a number of gastrointestinal problems, including heartburn, stomach pain, nausea, vomiting, and constipation (Danhof, Tr. 17301). The study results agreed with the literature that up to 10% of individuals taking aspirin report dyspeptic symptoms of upper gastrointestinal tract heartburn and stomach pain (Danhof, Tr. 17301–03). Dr. Danhof, respondent's witness, agreed that this study represents a growing trend associating gastric disturbances and ulcers with aspirin intake (Danhof, Tr. 17301).

988. Evidence also suggests that aspirin, while not the cause of all ulcers, may aggravate existing ulcers (Grossman, Tr. 7662, 7721; CX 466, p. 35390). Dr. Danhof testified that no one denies this fact (Danhof, Tr. 17304). In any given year, about 2% of the population or about 4 million persons have ulcers at any given time (Grossman, Tr. 7662, 7666). The actual number of persons having ulcers would be larger since the average patient with an ulcer experiences symptoms three years before a diagnosis (Grossman, Tr. 7666). All persons with ulcers should avoid aspirin (Grossman, Tr. 7660, 7721).

989. Gastric ulcers, like other ulcers, can become inactive. Because

the likelihood of recurrence is fairly high, there is a risk for those with inactive ulcers in using aspirin, since the aspirin might provoke the recurrence of the ulcer (Grossman, Tr. 7661). [247]

990. Aspirin also interferes with blood clotting, and should be avoided by persons with a history of blood coagulation defects, those receiving anticoagulant drugs, or those with severe anemia (CX 466, p. 35385).

991. The available data are not sufficient to demonstrate that the buffers or antacids in the amounts in Vanquish and Cope reduce the incidence of clinically important gastrointestinal effects (Grossman, Tr. 7493). Large amounts of antacids added to aspirin can reduce the topical action of aspirin in injuring the mucosa. However, the small amounts of antacid, such as those in Vanquish and Cope, are not sufficient to reduce the topical action of aspirin (Grossman, Tr. 7493). Further, the data are not sufficient to support the proposition that the possible speeding of disintegration and dissolution produced by antacids lead to decreasing side effects (Grossman, Tr. 7493). Consequently, products such as Cope and Vanquish, like unbuffered aspirin, are not recommended for persons suffering from adverse gastrointestinal effects since the same harmful effects could result.

992. The FDA OTC Analgesics Panel has recommended that the following warning appear on all aspirin-containing products, regardless of formulation: "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice or supervision of a physician" (CX 514, p. 35395).

2. Aspirin Intolerance Among Asthmatics and Respiratory Side Effects; Aspirin Allergies

993. Aspirin can also cause respiratory side effects. These adverse reactions include effects on the respiratory system ranging from shortness of breath to severe life-threatening asthmatic attacks, and anaphylactic shock involving laryngeal swelling, blocking of air pathways and sudden drop in blood pressure which can result in death unless treated rapidly (Stevenson, Tr. 1481; Farr, Tr. 2571–72; Falliers, Tr. 13558–59; CX 466, pp. 35397–98).

994. Asthma is a reversible obstructive airway disease of unknown origin. It is not a true allergy (Stevenson, Tr. 1479–80; Farr, Tr. 2656–66).

995. An asthmatic attack involves a spasm and subsequent constriction of the bronchial tubes. Symptoms include shortness of breath, coughing and, in severe cases, hypoxia (insufficient delivery of oxygen to red blood cells), shock, and occasionally death (Stevenson, Tr. 1481; CX 466, p. 35398).

996. Ingestion of anywhere from 3 mg to 650 mg of aspirin can cause

an asthmatic attack among susceptible members of the [248] asthmatic population (Stevenson, Tr. 1480). The severity of the aspirin-induced asthmatic attack depends on the degree of bronchial constriction prior to ingestion of the aspirin. If the bronchial tubes are already partly closed, the attack can be severe or even life threatening (Stevenson, Tr. 1489).

997. Combining aspirin with buffering ingredients, as in Cope and Vanquish, will not mitigate aspirin's asthmatic side effects (Stevenson, Tr. 1490–91; Farr, Tr. 2576).

a. *Incidence of Asthma*

998. While the number of asthmatics in the population is uncertain (Stevenson, Tr. 1493), Dr. Stevenson cited a 1972 article by Dr. Dorlan Davis, former director of the Allergic Disease Center of the National Institutes of Health which concluded that nine million persons were under medical care for asthma. This figure was determined by checking medical records at medical institutions, a method which Dr. Stevenson testified results in a reasonably accurate count of people under medical care for asthma. However, as there are a great number of asthmatic patients who are not part of the medical care system during any given period of time, this figure is an underestimate of the total number asthmatics in the United States (Stevenson, Tr. 1493–95; Falliers, Tr. 13549, 13551–52). Dr. Stevenson testified that the only way to obtain data of the total number of asthmatics in the United States is to carry out an epidemiological prospective study. A study by Dr. Irvin Broder published in 1974, the so-called Tecumseh study, an epidemiological study of health problems of the residents of a Michigan town, is the best evidence available on the incidence of asthmatics in the general population. It reported that 6% of the townspeople had conditions previously diagnosed as asthma and another 6% had medical histories consistent with asthma (Stevenson, Tr. 1494). Based on this study, which Dr. Stevenson feels is characteristic of the United States' population, Dr. Stevenson estimates there are 24 to 25 million asthmatics in the United States (Stevenson, Tr. 1494).

999. The 1974 Tecumseh study surveyed over 9,000 people. The diagnostic criteria for asthma included: (1) a report of asthma or wheeze; (2) associated with attacks of shortness of breath or trouble breathing out; (3) attributed to exposure to allergen(s); (4) diagnosed as asthma or asthmatic or wheezy bronchitis by the examining physician. Probably asthma was diagnosed when asthma or wheeze was reported along with at least two of the other features (2, 3, or 4) (Falliers, Tr. 13537–38). Dr. Constantine Falliers, Sterling's expert witness in the field of allergies, stated that the Tecumseh study was

a very thorough one which utilized "good clinical criteria" for determining the incidence of asthmatics (Falliers, Tr. 13256, 13536–39). Nevertheless, the Tecumseh findings are probably lower than the actual incidence of asthmatics in the general [249] population. An HEW report entitled "The Prevalence of Selected Chronic Respiratory Conditions" (RX 250–HEW) reported a 10% higher rate of asthmatics in the South and West than in the Midwest. Tecumseh, Michigan is located in the Midwest (Falliers, Tr. 13571–72; RX 250–HEW, p. 12).

1000. Respondent relied upon the HEW study, "The Prevalence of Selected Chronic Respiratory Conditions," RX 250–HEW, for support of the proposition that the incidence of asthma in the general population is as low as 3%. In fact, the HEW estimate of 3% is probably an underestimation of the incidence. According to the report, a number of factors should be considered in analyzing the data it contains. The report states and Dr. Falliers agrees, "reporting is better for those conditions which have made an impact on the affected individual and his family. Conditions that are severe or costly or require treatment tend to be better reported than conditions having lesser impact" (Falliers, Tr. 13543; RX 250–HEW, p. 1). The report goes on to say "the diagnostic accuracy of reported conditions is dependent on the information the respondent remembers that the attending physician has passed on to the family or, in the absence of medical attendance, on the previous experience or education of the family." Dr. Falliers agrees with this (Falliers, Tr. 13544; RX 250–HEW, p. 1). Therefore, taking into account the possibility that asthmatics with less than severe conditions had a low reporting rate, the whims of memory and possible self-misdiagnosis, the HEW study's prevalence estimate is probably underestimated. In addition, the report concludes that since the study omitted the institutionalized population, and the proportion of persons with chronic conditions in institutions is high, this also reduces the prevalence estimate (RX 250–HEW, p. 2).

1001. The 1937 study by Dr. Vaughan (RX 250–Vaughan), which studied the rate of incidence of asthma among the population of Clover, Virginia was cited by Dr. Falliers for his estimate that the incidence rate of asthma in the general population is 3% (Falliers, Tr. 13533). This is not a reliable or accurate study from which to estimate the incidence of asthma in the general population. The local study surveyed only 50% of the residents of Clover, Virginia (Falliers, Tr. 13533–34). The data reported in the summary is not broken down demographically in any way (Falliers, Tr. 13534–35). Further, Dr. Falliers testified that the study utilized a poor definition of asthma for diagnostic purposes and that the diagnostic techniques used may not be as current as those used today (Falliers, Tr. 13534).

1002. Dr. Falliers also pointed to the Service study presented in

summary form in the Vaughan article (RX 250–Vaughan) for support of the proposition that the incidence of asthma in the general population is as low as 3%. This study offers no support for this proposition. Information that is necessary for assessing the reliability and accuracy of such a [250] study, such as the definition used for diagnostic purposes and a demographic breakdown of subject's responses, is not included in the summary (Falliers, Tr. 13535–36).

1003. Various studies have found a range in the number of asthmatics in the United States population, depending on the nature of the population tested, the diagnostic and survey procedures used and these standards applied. While the number of asthmatics in the population is uncertain, it is not insignificant.

b. *Incidence of Aspirin Sensitivity Among Asthmatics*

1004. The exact incidence of aspirin sensitivity among asthmatics is not known (Falliers, Tr. 13549).

1005. Dr. Stevenson's own study, which challenged asthmatic patients not known to be sensitive to aspirin with aspirin, led him to conservatively estimate that 10% of the asthmatic population is sensitive to aspirin. Challenge studies are performed by exposing the patient to a substance and checking for reactions (Stevenson, Tr. 1471–73, 1498–99). A 4–year challenge study by Dr. Farr found 17.36% of asthmatics intolerant to aspirin, a figure he believed low because certain high risk subjects were excluded from the study (Farr, Tr. 2597–2604). The FDA Analgesics Panel estimated that between 6 to 20% of asthmatics are sensitive to aspirin (CX 466, p. 35397).

1006. Respondents relied upon an article by Drill (RX 250–Drill) for support of the proposition that the incidence of hypersensitivity to aspirin in the general population is .2%. Drill cited a .2% incidence rate but provided no references to the source of support for that estimate (Falliers, Tr. 13553).

1007. A number of factors should be considered when relying upon the results of historical studies. Respondent's witness Dr. Falliers agreed with the observation that historical studies are "subject to the whims of memory, the observer's skill in association of cause and effect and the historian's thoroughness and communicative skills." (Falliers, Tr. 11350–51). Further, historical studies rely on written medical records and exclude those people who are suffering from asthmatic symptoms who have not seen a doctor (Falliers, Tr. 13551–52). People who are hypersensitive to aspirin and have not exhibited any sensitivity and have not been challenged are likewise excluded. Medical records may also be incorrect. Many studies have shown that aspirin sensitive asthmatics do not necessarily exhibit the characteristics of being intrinsic nonallergic types with nasal polyps, bronchial

asthma and a history of aspirin intolerance, symptoms known as the "classic triad," and hence, may be mischaracterized as aspirin non-sensitive (CX 466, p. 35398; Falliers, Tr. 13556, 13561–67). Oral challenge studies in [**251**] general, reveal a higher incidence of aspirin sensitivity than historical studies. There are no oral challenge studies which support the low incidence rate reported in historical studies (Falliers, Tr. 13554–55). For all the aforementioned reasons, historical studies are flawed in a number of ways that tend to make them inaccurate and tend to underestimate incidence rates. Respondent relied upon a historical study by Gardner (RX 250–Gardner), and a 1971 article by DeWeck (RX 250–DeWeck–1972) for support of the proposition that the incidence of hypersensitivity to aspirin in the general population is .2%. The Gardner study was based on a 1940 poll of allergists and therefore contained no data from individuals who had not consulted a doctor or more specifically an allergy specialist. The DeWeck article relies in turn on two historical studies, the Gardner study and a study done by Bruce Pearson, a London clinical allergist, to support a .2% estimate of aspirin sensitivity (Falliers, Tr. 13552–54).

1008. Dr. Falliers testified that Dr. Max Samter's article published in 1968 in *Annals of Internal Medicine* titled "Intolerance to Aspirin" was the first published study which made the connection between aspirin sensitivity and asthmatic response (Falliers, Tr. 13551). Dr. Falliers states this is a very important discovery. Prior to publication of this discovery, medical records or case histories prepared by physicians would not have reflected a connection between asthmatic response and aspirin sensitivity (Falliers, Tr. 13551). Therefore, historical studies which relied on medical records recorded before Dr. Samter's discovery in 1968 would tend to be inaccurate and to underestimate incidence results. Gardner's historical study was done in 1940 (Falliers, Tr. 13552).

1009. While the exact incidence of aspirin sensitivity among asthmatics is not known, it is not insignificant.

c. *Allergic Reactions*

1010. Aspirin may also cause dermal allergic reactions, particularly urticaria (hives) and angio-edema (giant hives and swelling) (Stevenson, Tr. 1512; CX 466, p. 35398). Such reactions are not usually life threatening (Stevenson, Tr. 1511; CX 466, p. 35398), but urticaria may be serious if the lining of the stomach is involved, and angio-edema may be fatal if swelling takes place in the vocal chords, cutting off breathing (Stevenson, Tr. 1512).

1011. In some persons a few molecules of aspirin is sufficient to cause a dermal reaction, in others a relationship between dose and

severity has been seen (Stevenson, Tr. 1513). By contrast to asthmatic reactions, the incidence of dermal reactions is very small (Stevenson, Tr. 1464). [252]

1012. Preliminary animal findings have led some scientists to hypothesize that two types of impurities in aspirin may cause side effects in humans (Falliers, Tr. 13525, 13530). Dr. Falliers relied on three articles, RX 250–Bungaard, RX 250–Bungaard-Immunogenic, and RX 250–DeWeck–1971, to support his hypothesis that there is a correlation between the existence of two impurities in aspirin (acetylsaliylsaliylic acid (ASSA) and aspirin anhydride (ASAN)) and allergic reactions (Falliers, Tr. 13525–30). All three studies studied the effects of these impurities by administering them to guinea pigs (RX 250–DeWeck–1971, p. 393; RX 250–Bungaard, p. 122; RX 250–Bungaard-Immunogenic, p. 1). Legitimate questions about the use of guinea pig studies for drawing conclusions about a possible correlation between impurities in aspirin and allergic reactions in humans have been raised in the literature (Falliers, Tr. 13527–28). A letter to the editor written by allergists Paul Kalos and L. D. Schlumberger, which appeared in the *Journal of Pharmacy and Pharmacology,* 1978, states that since the method of administration to guinea pigs is never practiced in patients, Drs. Bungaard and DeWeck's results have no clinical significance in humans and any suggestion to the contrary would be misleading (Falliers, Tr. 13526–28).

1013. Dr. Falliers relied on the 1971 DeWeck study (RX 250–DeWeck (1971)) to support his hypothesis that there is a correlation between the amount of impurities in aspirin and allergic reactions in humans. This study does not establish a quantitative correlation between the amount of ASAN ingested in an aspirin tablet and its immunogencity in humans (Falliers, Tr. 13523–26). This is in large part due to the fact that the study failed to establish a correlation between the amount of conjugate given in a dermal method to humans in the study and the amount of aspirin anhydride, the impurity being tested, that might be ingested in an aspirin tablet. DeWeck states in his report that further studies will have to be made in humans in order to establish whether ASAN may be immunogenic in humans (Falliers, Tr. 13525; RX 250–DeWeck, p. 415). No follow-up studies to DeWeck's have been done. Further, since the 1971 DeWeck study, no studies have been published regarding the differences in sensitivity to different aspirin brands based on their differing amounts of ASAN (Falliers, Tr. 13525–26). There has been no correlation shown between the amount of acetylsalisylsalicylic acid (ASSA) and its immunogenic side effects in humans (Falliers, Tr. 13550). There is no scientific data to indicate a correlation between the amount of aspirin anhydride (ASAN) in an aspirin tablet and an

immunogenic reaction in humans. Nor is there any scientific reaction in humans. Nor is there any scientific data to indicate whether small differences in the amounts of ASAN will cause a measurable difference in response in a significant portion of the human population (Falliers, Tr. 13532–33). There has not been shown to be a correlation between the amount of impurities in aspirin and allergic reactions (Falliers, Tr. 13350, 13532–33). Current [**253**] evidence in fact suggests that impurities are not the cause of allergic responses to aspirin. Rather, the FDA OTC Analgesic Panel report states that "the mechanism involved in the intrinsic non-allergic aspirin-sensitive asthmatic probably includes the effect of aspirin on prostaglandin synthesis." (CX 466, pp. 35397–98). Dr. Falliers agreed that this is in fact the current theory (Falliers, Tr. 13603).

1014. The overall incidence and severity of allergic reactions to aspirin is such that the American Academy of Allergy, a professional organization with a membership of some 2,200 allergists, adopted the following resolution in 1973:

> While recognizing that acetylsalicylic acid (aspirin) is a valuable drug, the American Academy of Allergy recommends that a formulation containing aspirin and advertisements promoting the formulation should clearly indicate that the preparation contains aspirin and that aspirin can be harmful to some persons.

In the same year, the American College of Allergists, another professional organization of allergists, passed a similar resolution (Farr, Tr. 2608–12).

3. The Need for Aspirin Disclosure

1015. The FDA OTC Internal Analgesics Panel stated its agreement with the Academy resolution (CX 466, p. 35398). The Panel has recommended that the following warning should appear on all products containing aspirin:

> This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician. (CX 466, p. 35399).

1016. Because of the potential hazards to the fetus, as well as hazards to the mother during pregnancy and delivery, the FDA OTC Internal Analgesics Panel has suggested that all aspirin-containing products should state the following warning on their labels:

> Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician. (CX 466, p. 35356).

1017. Disclosure in advertising that Cope, Vanquish and Midol contain aspirin would be beneficial to the substantial number of people who, for sound medical reasons, should avoid [**254**] aspirin, and may not be aware that these products contain aspirin (Moertel, Tr. 6400; Grossman, Tr. 7487). There are large numbers of people who should avoid aspirin and are so warned (Moertel, Tr. 6354; Grossman, Tr. 7488). Dr. Stevenson testified, for example, that he warns patients whom he identifies as aspirin sensitive to avoid aspirin, but most asthmatics do not know if they are aspirin sensitive or not, and should avoid aspirin as a precaution (Stevenson, Tr. 1502). Immunologists generally warn asthmatics to avoid aspirin (Farr, Tr. 2601, 2606).

1018. However, many patients are not aware that an OTC product, which does not contain "aspirin" in its name, in fact contains aspirin. Because of this problem, some persons warned not to take aspirin will take it anyway (Stevenson, Tr. 1509; Falliers, Tr. 13574).

1019. The particular danger posed by aspirin unawareness was made clear, in Dr. Moertel's experience, when large numbers of his patients, whom he warned against aspirin-containing drugs, ingested analgesics unaware of their aspirin content. This subsequently caused gastrointestinal bleeding and hospitalization (Moertel, Tr. 6354–60).

1020. Disclosure of aspirin content on the label of a product is not a sufficient means of alerting persons who should avoid aspirin. In the experience of doctors testifying in this proceeding, consumers do not read labels on medications carefully, if at all (Grossman, Tr. 7487; Danhof, Tr. 17114–15).

1021. As respondent's witness Dr. Danhof testified: ". . . labels are almost worthless unless a physician or some other health professional specifically indicates to the patient he must begin reading labels. . . " (Danhof, Tr. 17114–15).

1022. It is particularly important to inform patients of the aspirin content of many OTC analgesics because "there is relatively little between the consumer and the medication" as compared to ethical drugs where there is at least a prescription and a pharmacist (Danhof, Tr. 17114–15).

1023. Moreover, Robert Chestnut, who has done research on consumers' awareness of label content, testified that a label is not an important source of information. His own research found little acquisition of information from packages. "By placing information onto a package panel, we engage in printing, nothing more" (Chestnut, Tr. 12447–48).

1024. Complaint counsel's expert Dr. Moertel conducted an informal survey of two samples of individuals with whom he came in contact in his duties at the Mayo Clinic in the recent past (Moertel, Tr. 6355–59). The first sample consisted of 100 patients and their

family members who came to the cancer [**255**] treatment center at the Mayo Clinic (Moertel, Tr. 6354–56). The second sample consisted of 100 paramedical personnel who, although nonphysicians, had some responsibility in dealing with medicine and worked in a medical setting (Moertel, Tr. 6356).

1025. Of the 100 patients and family members surveyed, 85% did not know that Cope contained aspirin and 3% incorrectly identified Cope as being aspirin. Of that same population, 63% were unaware that Vanquish contained aspirin and 2% incorrectly identified Vanquish as being free of aspirin (Moertel, Tr. 6360).

1026. A substantial number of consumers do not know that Vanquish contains aspirin. The 1970 Vanquish study (CX 404) indicates that only 15% of the consumers interviewed knew Vanquish contained aspirin (Hall, Tr. 9227–28).

1027. Moreover, a 1970 Analgesic Segmentation study done for Glenbrook Laboratories indicated that four out of five people have *no* idea what ingredients are in the brand of pain reliever they use most often (CX 394A).

1028. The fact that Cope, Vanquish and Midol contain aspirin is a material fact (F. 974–1014, *supra*). It is of great importance to a substantial number of consumers who might otherwise be misled into purchasing and ingesting aspirin, and it should be disclosed in advertising as alleged in Complaint Paragraphs 23, 24, 25.

K. *Cope's Unique Formula (Complaint ¶ 22)*

1029. Respondent represented that Cope contained a unique formula because it alone among nonprescription headache remedies contained a pain reliever and an ingredient with sedative properties.

1030. Internal memoranda circulated at Glenbrook Laboratories in March 1969 indicate that respondent was aware that Bristol-Myers was test marketing a product, Excedrin P.M. (CX 357A; CX 678, admission 1069). The memoranda included a fact sheet on the product which details the Excedrin P.M. formula (CX 357B).

1031. The Excedrin P.M. formula is described in the Glenbrook Laboratories memo as including *inter alia* aspirin and methapyrilene fumarate (CX 357B). Methapyrilene fumarate is an antihistamine which may have sedative side effects, and is included in the Cope formula.

1032. Because Sterling claimed that Cope was a unique formula when it knew Excedrin P.M. contained the same analgesic and the same ingredient with sedative properties, the advertising claims were misleading in a material respect, as alleged in Complaint Paragraph 22. [**256**]

V. EVIDENCE RELATING TO BAYER MANUFACTURING PROCESS AND QUALITY CONTROL IS INSUFFICIENT TO SUPPORT BAYER'S PHARMACEUTICAL OR THERAPEUTIC SUPERIORITY CLAIMS

A. *Significance of Quality Control and FDA Good Manufacturing Practices in the Manufacture of Aspirin Tablets*

1033. It is well recognized in the medical profession that quality control standards are important because of their therapeutic implications. The purpose of quality control is to insure the fitness for use of the drug product, not only at the time of manufacture, but through the end of the shelf life. Quality control guarantees the reliability of drug products and insures that they will perform as expected.

1034. The central aspect of quality control is the reduction of variable factors. This is significant because our understanding of formulation and processing factors which may affect therapeutic efficacy is incomplete. Factors previously thought to be insignificant, have now been shown to be deleterious.

1035. The FDA recognizes in its Good Manufacturing Practices regulations (GMP's) that product and manufacturing characteristics are related to the safety and efficacy of drug products (Rhodes, Tr. 11155). The FDA's Good Manufacturing Practices regulations, 21 C.F.R. 200–299, were established in order to control the quality of drug manufacture in this country by implementing broad guidelines relating to the organization of quality control units, qualifications of persons involved in the manufacturing process and the buildings, facilities, equipment, materials, processes, packaging, handling, labeling, and laboratory controls involved in the process of drug manufacture. The GMP's are guidelines, and therefore it is up to the company to use their expertise to meet the intent of the guidelines within their own specific manufacturing practices. By the same token, the GMP's do not insure that all drug products will be of the same quality (Banker, Tr. 12572–76).

1036. The underlying philosophy of the FDA GMPs is to give manufacturers some flexibility to set their own specifications that meet or exceed those required by the USP or by the FDA. However, once these specifications are approved by the FDA, a company might be in violation of FDA regulations if it fails to comply with its own specifications (Rhodes, Tr. 11157; Winig, Tr. 13684).

1037. The concept of *validation* which is embodied in the Good Manufacturing Practices requires that manufacturers look at every factor likely to affect the quality of drug products during the manufacturing process. Drug manufacturers must then [**257**] prepare standard operating procedures so that the whole process is precisely controlled. *Optimization* recognizes that pharmaceutical dosage

forms are complex physicochemical systems, and that oftentimes the best product that you can produce will to some extent be a compromise. Optimization involves the search for the best formulation which will satisfy a number of sometimes conflicting demands (Rhodes, Tr. 11155–57; Banker, Tr. 12577, 12606).

1038. FDA policy favors the optimization of drug products. Optimization necessitates a balancing of parameters for drug products. An optimized aspirin tablet would have a rapid disintegration rate, and disintegrating particles would be in a fine state of subdivision. At the same time, the tablet should not break in the bottle and should be resistant to moisture. These factors present a number of competing objectives. For example, while increasing the hardness might reduce the resistance to water vapor, it would also reduce porosity and disintegration. Therefore, a balancing of factors is necessary (Banker, Tr. 12565–77).

1039. RX 250, *FDA, Introduction to Total Drug Quality* (DHEW Pub. No. (FDA) 74–3006) (November 1973) is an official publication of the FDA setting forth its regulatory policies and procedures governing New Drug Applications (Scoville, Tr. 14349–50, 14357). In determining whether to grant a new drug application, the FDA requires in addition to clinical demonstration of efficacy and so forth, a substantial amount of nonclinical data relating to pharmaceutical, chemical and manufacturing characteristics (Scoville, Tr. 14351–65, 14369–71; RX–250, *FDA Introduction to Total Drug Quality,* pp. 5–8, 24–34).

1040. It is the position of the FDA that physical and chemical characteristics of a drug product can have an important bearing upon the therapeutic performance and safety of that drug product. Examples of these physical and chemical characteristics include stability, content variation, disintegration, time, purity (Scoville, Tr. 14446).

1041. The types of physical, chemical and manufacturing tests and data required by the FDA include:

(i) identity, source, and variation of all ingredients, from raw materials to final dosage stage (Scoville, Tr. 14353–54; RX 250, *FDA, Introduction to Total Drug Quality,* p. 6).

(ii) physical and chemical information, including including variation in impurities, relating to all ingredients on a per tablet and batch basis, including nonactive ingredients such as excipients **[258]** and lubricants (Scoville, Tr. 14354–55; RX 250, *FDA, Introduction to Total Drug Quality,* p. 6).

(iii) information describing the methods of manufacturing, manufacturing, processing and packaging of drugs, including quality control measures (Scoville, Tr. 14355, 14357–61; RX–250, *FDA, Introduction to Total Drug Quality,* pp. 6–7).

(iv) data relating to labeling of the drug product (Scoville, Tr. 14361–63; RX 250, *FDA, Introduction to Total Drug Quality,* p. 6).

(v) data relating to stability of the drug (Scoville, Tr. 14363; RX 250, *FDA, Introduction to Total Drug Quality,* p. 20).

1042. Among the nonclinical data required by the FDA in evaluating a new drug application, are FDA scientific literature relating to the product; clinical reports; open-end studies; pharmaceutical and chemical testing; physical observations; blood level studies; information relating to the manner in which the product is metabolized (Scoville, Tr. 14346–47).

1043. Approximately two-thirds of the new drug applications which are rejected by the FDA are rejected not due to problems with clinical testing, but rather due to deficiencies relating to the pharmaceutical properties of the drug and/or the manufacturing processes (Scoville, Tr. 14366). The Director of the FDA's Office of New Drugs, Dr. Robert Hodges, reported in the *American Journal of Hospital Pharmacy* in 1968, at p. 121, in an article entitled, "Biopharmaceutic Equivalency and the Role of the Food and Drug Administration," that among the new drug applications rejected by the FDA, over 70 percent were found unacceptable due to deficiencies relating to such factors as: too great a variation in amount of active ingredient; particle size; crystal form; solubility; labeling; processing; packaging; weight variations; *in vitro* release patterns; impurities, including trace metals; and stability (Scoville, Tr. 14367–68; RX 250, Hodges, "Biopharmaceutic Equivalency and the Role of the Food and Drug Administration," *Am. J. Hos. Pharm.,* 25:121 (1968)). Rejection of new drug applications due to inadequate information or deficiencies relating to such pharmaceutical and manufacturing factors reflect the FDA's determination that these factors are essential in assuring the safety and efficacy of the drug (Scoville, Tr. 14368–69).

1044. It is the position of the FDA that "the most important single factor in producing a satisfactory drug product is the quality of the manufacturing practices applied." (Scoville, Tr. 14375; RX 250, Hodges, "Biopharmaceutic Equivalency and the Role [**259**] of the Food and Drug Administration," *Am. J. Hos. Pharm.,* 25:121, at p. 127 (1968)).

1045. The FDA's regulation of drug products does not always result in all brands of the same drug product being pharmaceutically equivalent (Scoville, Tr. 14388). Mere fact that the same drug made by two different manufacturers meets GMP standards does not guarantee that the drugs will be therapeutically equivalent (Scoville, Tr. 14388, 14390–91, 14407).

1046. During the early 1970's, a panel of distinguished experts studied USP standards and the FDA's Good Manufacturing Practices

regulations to determine whether these standards assure quality and uniform bioavailability for drug products. (Scoville, Tr. 14409–10) The report, Office of Technological Assessment, Drug Bioequivalency Study Panel, *Drug Bioequivalence* (1974) (RX–158) [official notice was taken of this document] concluded that:

> Present compendial standards and guidelines for current good manufacturing practices do not ensure quality and uniform bioavailability for drug products (Scoville, Tr. 14410 –12; RX 158G).

The report further concluded that:

> The guides for current Good Manufacturing Practice should be expanded to include specific descriptions of all scientific aspects of manufacturing processes from the raw materials to the final product.

1047. The FDA has set up a program to evaluate for labeling the safety and efficacy of OTC drugs by establishing separate monograph panels of experts to review those drugs (Scoville, Tr. 14451). The Internal Analgesic Panel has reviewed aspirin and issued a report, CX 466. The rules governing this and all other product monograph panels are set forth in 21 C.F.R. 330.1–.12 (April 1, 1979) (Scoville, Tr. 14451–52).

1048. The regulations governing procedures to be employed by the FDA-OTC drug review panels, including the Internal Analgesic Panel, expressly provide for nondouble blind clinical data to be used, along with controlled studies, in evaluating the therapeutic performance of a drug. 21 C.F.R. 330.10 *et seq.* (April 1, 1979). Under "Efficacy Data" to be considered by the panel are: "Controlled Studies;" "Partially Controlled or Uncontrolled Studies;" "Documented Case Reports;" "Pertinent Marketing Experiences That May Influence a Determination on the Efficacy of Each Individual Active Component;" "Pertinent Medical and Scientific Literature." (Scoville, Tr. 14457–58). The regulation further provides (Part VI of 330.10) that **[260]** conclusions may be reached as to the therapeutic efficacy of a drug product in the absence of any controlled studies (Scoville, Tr. 14458–59).

1049. Prior to undertaking its task, the Internal Analgesic Panel was briefed by the FDA's General Counsel as to the type of evidence which may be considered by the Panel to reach conclusions regarding the efficacy of the drugs reviewed. The Panel was advised that it may consider evidence other than well-controlled, double-blind clinical testing in the absence of well-controlled clinical studies (Scoville, Tr. 14453–57; RX 419).

1050. Complaint counsel have admitted that the conclusions

reached in the preliminary report of the FDA/OTC Internal Analgesic Panel are not all supported by well-controlled clinical studies (RX 413V, Complaint Counsel's Admission No. 392). Complaint counsel have also admitted that the conclusions of the FDA Internal Analgesic Panel have a reasonable basis although they are not all supported by well-controlled clinical studies (RX 413W, Complaint Counsel's Admission No. 393).

1051. Other FDA review panels have occasionally made medical judgments based on grounds other than double-blind clinicals (Scoville, Tr. 14465).

1052. The Topical Otics Panel is one of the panels established by the FDA to review OTC drugs, like the Internal Analgesic Panel (Scoville, Tr. 14474–75). The Otics Panel report discloses that this panel made therapeutic judgments as to the efficacy of some products, such as an ear wax softening agent, relying upon data other than that obtained from well-controlled, double-blind clinical tests. This data included clinical use and marketing experience. 42 FR 63556 at 63562, 63563 (December 16, 1977) (Scoville, Tr. 14474–76). However, where a manufacturer added benzocaine to its product and made the "additional" simple claim of effective relief from "Minor irritations caused by wax, itching and other discomforts," the Panel concluded the product was not effective as claimed due to the absence of clinicals. 42 FR 63556, 63557.

1053. The Antacid and Antiflatulent Products Panel is an FDA-OTC panel like the Internal Analgesic Panel (Scoville, Tr. 14476–77). The work of that Panel has led to a final order, adopted by the FDA. 39 FR 19862–77 (June 4, 1974). This final order, establishing an *in vitro* test as the sole measure for determining efficacy of antacid products, is consistent with the FDA's acceptance of *in vitro* methodology where appropriate (Scoville, Tr. 14481). The Panel and the FDA agreed, however, that a claim of *superior efficacy* required not only support through *in vitro* tests, but through "studies [showing] that the antipeptic activity is clinically meaningful [**261**] and therefore contributes to the product's effectiveness." 39 FR at 19873.

1054. The FDA has a drug monitoring program through which it tries to assure that the minimal compendial standards and good manufacturing practice regulations are complied with. If the compendial standards are not met, the FDA may order the product recalled or seized (Scoville, Tr. 14429, 14432–33; RX 152). One aspect of this drug compliance enforcement mechanism is plant inspections by FDA officials (Scoville, Tr. 14429–30; RX 250, *FDA, Introduction to Total Drug Quality,* pp. 58–67). Plant inspection involves an FDA field inspector going through a plant to check for all facets of quality control such as proper functioning of equipment like tablet depressors, purity

of raw materials, proper labeling and packaging procedures and facilities (RX 250, *FDA, Introduction to Total Drug Quality,* pp. 60–67). Another aspect of enforcement is the monitoring of drugs in the marketplace to determine whether the compendial standards are being met (Scoville, Tr. 14432).

1055. It is recognized that the FDA's plant inspection program does not prevent deficiencies relating to all marketed drug products. Due to monetary restrictions, the FDA has insufficient resources in manpower and otherwise to effectively monitor all manufacturing facilities (Scoville, Tr. 14430). Accordingly, the FDA has utilized its limited manpower to concentrate on inspecting plants which produce prescription drugs rather than over-the-counter drugs (Scoville, Tr. 14430–31).

1056. It is recognized that the FDA's monitoring program of drugs in the marketplace for compliance with compendial standards is not stringent. As a practical matter, only a small proportion of drugs, including aspirin, which fail to meet legal requirements, would be discovered by the FDA and would be removed from the marketplace (Scoville, Tr. 14437). Thus, the recalls, seizures and judgments of aspirin tablets for failure to comply with legal requirements during the period 1967–1977, RX 152, may constitute a small part of defective aspirin tablets actually on the market (Scoville, Tr. 14437).

1057. For a 10–year period, from September 1967 through January 1, 1977, the FDA recalled, seized, or obtained judgments against approximately 30 different plain aspirin products (Scoville, Tr. 14433–37; RX 152). Recalls, seizures or judgments were obtained against the aspirin products for such reasons as: "below USP quality standard," "fail to disintegrate," "no sore throat warning statement" (Scoville, Tr. 14433; RX 152B); "prepared, packed and held under insanitary conditions" (Scoville, Tr. 14434; RX 152M); "labeling lacked adequate directions for use and adequate warning against accidental ingestion or overdose by children" (RX 152Q); "fails USP weight variation requirements" (RX 152S); [**262**] "fail to disintegrate" (RX 152V); "short count on number of tablets in bottles" (Scoville, Tr. 14434; RX 152Z001); "subpotent" (RX 152Z003); "none of the tablets tested disintegrated in five minutes." (Scoville, Tr. 14434–35; RX 152 Z001).

1058. Various of these recalls by the FDA, such as for failure to meet USP disintegration test standards, have resulted in the product being recalled under a "Class II" category of recall, which is defined as "a priority situation in which the consequences may be immediate or long-range and possibly or potentially life-threatening or hazardous to health." (Scoville, Tr. 14435–36; RX 152Z015).

1059. Complaint counsel have admitted that the existence of laws and regulations concerning pharmaceutical quality does not ensure

that every manufacturer complies with such laws and regulations at all times or on all occasions (RX 413 T, Complaint Counsel's Admission No. 372).

1060. The inadequacy of the FDA's enforcement program relating to OTC drugs is general knowledge in the drug industry (Scoville, Tr. 14438–41). Dr. Richard Crout, the then Deputy Director and now Director, of the Bureau of Drugs of the FDA, which regulates all drugs including aspirin, stated, in a public speech delivered at the Ohio State University College of Pharmacy in 1972 (Scoville, Tr. 14439–40):

> There is essentially no monitoring of the quality of over-the-counter drug products in this country.
>
> As you know, the Food and Drug Administration is undertaking a review of all over-the-counter products for safety and efficacy, but unless there is a very major expansion of our laboratory and inspectional resources, the production quality of over-the-counter products will continue to go unmonitored

Because of the FDA's inability to effectively monitor drugs, the integrity of the drug manufacturer is of great importance (Scoville, Tr. 1444–45).

1061. The former medical director of the Food and Drug Administration has publicly stated, in an address to the American Pharmaceutical Association, reported in Ulrich, "The Generic Drug Dispute in Louisiana," *J. Louisiana Med. Soc.,* 117:141, 149 (1965):

> The naive belief that if a product was not good the FDA would prohibit its sale is just not realistic. FDA labors long and [**263**] diligently to protect the public, but the fact of the matter is that it's completely impossible for FDA to check every batch of every product of every manufacturer that is marketed. Hence, the integrity and reputation of the manufacturer assume unusual significance where drugs and health products are concerned (Scoville, Tr. 1444).

1062. Bayer Aspirin and Bayer Children's Aspirin have never been the subject of any FDA enforcement proceedings (Scoville, Tr. 14436–37).

1063. 21 C.F.R. 202.1(4)(b)(3)(iii) sets forth the FDA's requirements for substantiation for aspects of prescription drug advertising. According to Dr. Scoville, one type of substantiation which may justify claims in an advertisement is the opinion of experts (Scoville, Tr. 14575) 21 C.F.R. 202.1(4)(b)(3)(iii)(a).

1064. According to Dr. Scoville, who is not an expert on FDA regulations governing drug advertising substantiation, Part (b) of the same regulation permits as an alternative, substantiation to be based solely upon clinical investigations. Clinical investigations include double blind clinical testing if appropriate. There are other types of clinical trials which would satisfy the substantiation requirements for pre-

scription advertising under this provision. Dr. Scoville also testified that Part (c) of the same regulation sets forth another class of substantiation materials which would be sufficient to support an advertising claim (Scoville, Tr. 14576). This substantiation consists of substantial clinical experience which is adequately documented (Scoville, Tr. 14575–77, 14595).

1065. 21 C.F.R. 202.1(6)(i) of the FDA regulations applicable to prescription drug advertising governs false or otherwise misleading advertising. This section provides that advertising claims should not exceed the evidence submitted in support of that claim (Scoville, Tr. 14578). According to Dr. Scoville, the section does not govern comparative advertising in the sense of comparing one brand of a drug against another brand of that drug or a comparison of different drug products (Scoville, Tr. 14535–35).

1066. 21 C.F.R. 202.1(6)(ii) of the FDA regulations governing prescription drug advertising relates to false or misleading advertisements of a comparative nature. The principal purpose of this provision is to govern substantiation for advertisements where one prescription drug is being offered as a superior substitute for a different prescription drug (Scoville, Tr. 14549–51, 14578–81). The regulation declares advertisements misleading which state a drug is more efficacious than another drug when it has been not so demonstrated by "substantial evidence or substantial clinical experience." **[264]**

1067. These rules are most closely analogous to the issues in this case, as FDA does not regulate OTC Drug Advertising:

> (6) Advertisements that are false, lacking in fair balance, or otherwise misleading.
>
> An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of Section 502(n) of the act among other reasons, if it:
>
> (ii) Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.

Substantial evidence as referred to is defined in Section 202.1(e)(4)(iii)(b) and (c) as "evidence consisting of adequate and well-controlled investigations including clinical investigations." Clinical experience is defined to mean, in the case of drugs intended for administration to man, "investigations, experience or significance in humans." *Id.*

B. *Bayer Manufacturing Process and Quality Control Standards*

1068. At trial, Mr. Jerome Winig, a retired Sterling official, testified

regarding the Bayer manufacturing process and quality control procedures. *See* F. 164–167, *supra.*

1069. Bayer Aspirin powder is manufactured from salicylic acid, acetic anhydride, special naptha, and an organic wash solvent, cyclohexane. Acetic anhydride converts the salicylic acid into an ingestible acetylsalicylic acid. Naptha is used to permit a homogenous mixture and to serve as a precipitant (Winig, Tr. 13624).

1070. Cornstarch is another raw material used. The cornstarch used by Sterling is prepared according to Bayer's own specifications, which involves a trade secret. According to Mr. Winig, there are standards for whiteness, freedom from foreign matter, and moisture content control (Winig, Tr. 13626).

1071. Aspirin tablets must contain a disintegrant which takes on water and allows the tablet to explode in the gastric fluid, releasing aspirin particles. This creates a problem [**265**] because a good disintegrant has a high affinity for water and will tend to draw it into the tablet, increasing the dangers of decomposition. Dr. Banker testified that Bayer has a unique process by which a special grade of starch with a lower equilibrium moisture content and less affinity for water is employed while retaining the ability to explode in the presence of moisture (Banker, Tr. 12613–14).

1072. According to Mr. Winig, the Bayer process starts with high quality materials. Bayer also has thorough quality control for incoming materials and completed products. During the manufacturing process of Bayer Aspirin powder, the raw materials are combined, agitated, heated, cooled, washed, filtered, and dried. Throughout the process, stainless steel and aluminum utensils are used and precise rates of cooling, heating and agitating are necessary (Winig, Tr. 13627–30).

1073. In producing aspirin powder, the principal steps are acetylation and crystallization. Thereafter, in producing tablets from the powder, the principal steps are blending the aspirin crystals together and with an excipient, slugging, and tableting. Acetylsalicylic acid, or aspirin, is synthesized by chemically combining salicylic acid with an acetyl radical, which may come from either acetic anhydride or acetyl chloride. This is called the acetylation process. The first step in the manufacture of Bayer Aspirin is to "charge" or fill a stainless steel reactor kettle with accurately measured amounts of the basic raw materials (acetic anhydride, salicylic acid, and a special naptha). The kettle is heated by the circulation of hot water through a steel jacket which surrounds the kettle. The chemical reaction of acetylation takes place at elevated temperatures over a period of about six hours. The solution is then cooled and crystallization occurs—acetylsalicylic

acid crystals are precipitated out of the solution (Winig, Tr. 13624–25, 13627–28).

1074. Mr. Winig testified that in acetylation and crystallization, several of Bayer's exclusive trade secrets and know-how come into play. One Bayer trade secret is the specific temperatures at which the material is acetylated. A second is the controlled rate at which the precipitation of the acetylsalicylic acid crystals occurs. By close and careful temperature control, it is possible to keep any impurities in solution while the aspirin is precipitated out. Also, by control of the temperatures and rates of heating during acetylation and by control of the rate of cooling, it is possible to produce several kinds of aspirin crystals. A third lies in the selection of the naptha fraction and the technique of using the naptha medium, to serve the functions of a diluent, a precipitant and an agent for removal of impurities (Winig, Tr. 13627–30).

1075. In the next step, the aspirin crystals are washed with an organic solvent spray. There are repeated inspections and **[266]** rewashing, and then a carefully controlled drying operation. At the end of a four-day process, there are dried separate batches of aspirin crystals of the two special types—the needle crystal and the flake crystal. These crystals are examined and tested in the Bayer Control Laboratory for quality, purity and strength. If the crystals satisfactorily pass such tests, the two types are then blended in specific proportions, and the resultant product is mixed and blended with an excipient. An excipient is a material other than the active drug which is added to a dosage form for various purposes. In Bayer Aspirin tablets, the only excipient is cornstarch which serves as a binder and a disintegrator. Upon contact with water, the cornstarch promptly explodes in a cloud-like dispersion, permitting a fine release of aspirin in crystals, rapidly, uniformly gently and smoothly. In particular, to control the moisture content of cornstarch, Sterling prescribes minimum 10%, maximum 12%. A controlled moisture content is important because too much water in the cornstarch will produce a tablet which is undesirable for hardness while too little moisture results in a tablet which crumbles easily. The cornstarch is important in the rate and nature of disintegration of the Bayer tablet (Winig, Tr. 13629–31, 13636).

1076. According to Mr. Winig, in the blending of the needle and flake crystals in a specific proportion, and the excipient, the goal is to produce tablets with uniform fine particles and an intimate mixture of aspirin and cornstarch throughout the tablets. Bayer seeks to achieve this by blending the aspirin and starch, and by processing the blend through an attrition mill, then sieving through very fine silk mesh screens. By means of the attrition mills, the aspirin crystals are

gently rubbed against each other to achieve a particular size. The crystals are not allowed to fracture or break off.

1077. After the material is screened, or bolted, it is sent to giant compressors or slugging machines. The slugs, or large tablets, that are produced are about 16 times the size of the tablets sold to the public and weigh about 100 grains. Through this slugging process, Bayer seeks to achieve a granulation which insures a uniform composition, hardness and rate of disintegration in the final tablet. The slugs are then reground to a carefully controlled granulation of a specific screen or mesh size. These granules are fed into a rotary tableting machine which presses out tablets under pressure. Sixteen different laboratory tests are carried out on the samples representative of each tablet compressor for each day's production. The tablets are permitted to age and they are then again inspected. The tablets are then mechanically bottled or tinned (Winig, Tr. 13634).

1078. Respondent's witnesses testified that the Bayer manufacturing process is unique because it employs a batch [**267**] method, a nonaqueous process, achieves fine uniform particle sizes, uses two crystal forms without a lubricant, and includes over one hundred quality control tests (*see, e.g.*, Rhodes, Tr. 11309–15; Banker, Tr. 12610–14, 12616; Winig, Tr. 13634, 13637–39, 13648, 13663–67).

1079. According to Mr. Winig, there are differences in the manufacturing processes of Bayer and other aspirin producers. Bayer uses a single bath, noncontinuous process. Use of the bath method provides a clean setup every time a new batch is started. This allows exercise of close quality control (Winig, Tr. 13637).

1080. Recycling the "mother liquor" which Bayer avoids by using a one bath process, is a term used to mean that when a new chemical is made, the resulting portions of the original chemicals which are not included in the finished chemicals are left behind to be used in the next batch (Winig, Tr. 13641).

1081. Bayer uses a nonaqueous process. Since aspirin is an organic ester, it is readily subject to hydrolyzation which is provoked by water, elevation of temperature, or alkali. A nonaqueous process builds a greater stability into the product. This procedure was originally patented in 1900 and has been refined and improved since then. According to Mr. Winig, Dow also uses organic solvent which is nonaqueous (Winig, Tr. 13636–39).

1082. Dr. Banker has personally inspected the Bayer Aspirin Manufacturing Plant in Trenton, New Jersey. During the course of his inspection, he observed the manufacturing process and quality control procedures according to which Bayer Aspirin and Bayer Children's Aspirin are manufactured. He observed that Bayer uses no lubricant in the manufacture of its aspirin. There are two crystal

forms of aspirin that are employed in the manufacture of Bayer Aspirin—a needle form and a flake form. According to Dr. Banker, the manufacturing process for Bayer Aspirin is unique. Bayer makes their own aspirin. Bayer uses a special process to create unique particles, which are very fine, and aid in the production of Bayer's unique disintegration-dissolution profile. Bayer creates these very fine particles through processes that combine the two crystal forms of aspirin in a special grade of starch which has an unusually low moisture content, and is available from only a single supplier. These materials are combined in a machine called a muller, which employs crushing rolls in combination with a mixing container. The operation of this machine produces what is known as pharmaceutical extinguishing, where one material is smeared over the surface of the aspirin particles. According to Dr. Banker, conventional aspirin is all needle form, and therefore a lubricant must be used (Banker, Tr. 12610–14).

1083. According to Dr. Fields, aspirin manufactured by a nonaqueous procedure provides a more rapid de-acetylization. [268] The acetyl radical prevents coagulation or blood clotting. In order to get this effect as promptly as possible, it is necessary to have a rapid release of the acetyl radical from aspirin. Aspirin affects platelets in the blood by a process of acetylization. The acetyl radical membrane around these blood elements which are normally disc-shaped and prevents them from expelling their contents—the various chemicals that are contained within them. This is called acetylization of the platelet basement membrane. By doing this, aspirin will have an effect on the platelet membrane, and this acetylization is permanent for the life of those platelets. Platelets are made in the bone marrow, circulated in the bloodstream, and destroyed in from five to seven or eight days in the spleen. Thus, it is important to have a rapid release of the acetyl radical from aspirin in order to get the effect as promptly as possible. Salicylic acid does not affect clotting of blood. Anti-inflammatory drugs, such as Indomethacin, Butazolidene, and Sulfimpyrazone, do not act in the same manner as aspirin. If there is a rapid removal of the acetyl radical from acetylsalicylic acid, there is rapid acetylization of the platelets, and this is desirable for preventing clotting (Fields, Tr. 16594–96).

1084. According to respondent's witnesses, aspirin tablets are normally made by a wet granulation technique, which includes a mixing of the drug and other excipients with either water or an alcohol-water mixture. The problem with this is that aspirin is very liable to hydrolysis. Therefore, there is a distinct advantage in having a manufacturing procedure in which the drug is not exposed to water. According to Drs. Banker and Rhodes, all of Bayer's competitors expose their drug product to either water or a water-ethanol mixture (Rhodes, Tr.

11311–92; Banker, Tr. 12011; RX 170; RX 413, complaint counsel's admission nos. 403, 404, and 405).

1085. RX 218, a letter from Dr. Cooke of the USP Revision Committee to the Mellon Institute refers to the problem of hydrolizing aspirin: "Moisture is not supposed to be used in preparing the granulation, but rather the dry slugging process." This statement favors a nonaqueous process, which Bayer has at all stages, not just at the stage of preparing the granulations (RX 218).

1086. Mr. Winig has visited the Monsanto plant. According to Mr. Winig, Monsanto uses a water wash process and a recycling process as opposed to the single bath method used by Bayer.

1087. Mr. Winig has visited the Dow plant. According to Mr. Winig, Dow uses organic solvents which are nonaqueous. Mr. Winig also testified that Norwich uses an aqueous process (Winig, Tr. 13639–40). Thus, evidently the nonaqueous process is not unique to Sterling. **[269]**

1088. The formula for Bayer Aspirin indicates that Bayer Aspirin contains no lubricant, such as magnesium stearate. According to Drs. Banker and Rhodes, respondent's witnesses, this is an advantage to Bayer for two reasons. First, magnesium stearate is a substance whose presence is disadvantageous from the point of view of aspirin stability. Second, the percent of active drug within the tablet is 80%. That means that it is easier to establish and control the purity in the amount of the final aspirin content in the tablet, because there is such a high percentage of active drug (Rhodes, Tr. 11309–11; Banker, Tr. 12616; RX 170).

1089. RX 169 *in camera,* "Reference File, Quality Control Procedures" outlines the steps taken by the quality control group. The quality control group issues control numbers to products. The system has been in use since at least 1935 and enables Sterling to identify the particular lot number and raw materials used in producing a particular bottle of a product. RX 169F indicates the point in the process at which quality control samples are taken. The quality control group attaches labels such as "released" and "rejected" during this process. Identification numbers are used to identify the aspirin powder (Winig, Tr. 13658–60; RX 169).

1090. RX 170 *in camera,* "Glenbrook Laboratories, Bayer Five-Grain (324 mg.) Aspirin Tablets, Analytical Tests, September 1970" details the laboratory procedures for the analytical tests which are required for virtually everything that goes into the Bayer operation. There are 115 laboratory tests which occur during the process. They are performed on all substances from raw materials through finished products. In addition, there are 43 tests which are done in the Bayer

laboratories to confirm tests done by suppliers, including packaging tests (Winig, Tr. 13662–63).

1091. Specifications for aspirin powder and the procedures to be used in testing for those specifications are also listed. Some of the procedures are USP procedures, and if different but equivalent procedures are used, it is only with the express approval of the Food and Drug Administration. The specification for the cornstarch is a minimum of 10% and maximum of 12%, as determined by the Karl Fisher titrametric method. Aspirin tablet mix procedures are outlined. The relative proportions of needle and flake crystals are a trade secret (Winig, Tr. 13664–66).

1092. Bayer assigns control numbers to each day's tableting rather than each day's packaging. Bayer's method keeps a more exact tabulation of each bath. The system used to retain samples is a referee sampling system. Unopened packages for each control number are retained for a period of five years. At the end of that time, two of the samples for each month are selected to be retained indefinitely, while the others undergo **[270]** stability testing. From a control number, it is possible to know all the mixtures, analysis, and raw materials which are in any particular bottle of Bayer Aspirin (Winig, Tr. 13666–69).

1093. RX 170Z015 states the Bayer quality control specifications for 5–grain aspirin tablets, and RX 170Z034 is the report form on which the results of these tests are given. RX 170Z042 and Z043 compare USP standards and Bayer standards for aspirin tablets and aspirin powder. Charts plot the variation in measurement of content, disintegration time, and weight for each control number (Winig, Tr. 13663–70; RX 170).

1094. Sterling's quality control procedures and the specifications set forth in RX 170 are in effect today, and were in effect between 1969 and 1974. RX 170 is important in assessing the pharmaceutical quality of Bayer Aspirin and Bayer Children's Aspirin (Winig, Tr. 13676–77; RX 170; RX 171).

1095. RX 151 shows how USP standards for aspirin powder and tablets have changed from 1927 through 1975. It also compares the USP standards with the Sterling's own standards for Bayer Aspirin. For example, with respect to the standard for aspirin content, USP originally had no standard whereas Bayer had a standard of 100–105%. It is notable that the Bayer standard remained invariant from 1926 through 1975 whereas the USP standard has gradually improved. The standard for USP is presently 95–105% (Rhodes, Tr. 11231–33; Banker, Tr. 12620–25; Tainter, RX 2840; RX 151).

1096. USP standards have changed over the years. Most of the changes are in the direction of a gradual tightening in the areas of

disintegration, aspirin content, and weight variation. The USP standard for FSA was relaxed for aspirin tablets. Sterling had objected to it when its opinion was solicited. The USP reason for the change was that half of the manufacturers of aspirin tablets had difficulty in meeting the existing standard (Klumpp, RX 285Y). Thus, the Director of USP REVISION, Lloyd Miller, Ph.D., wrote Sterling's Director of Control that USP data indicated that even the new FSA standards "will challenge the skill of at least one-half of the makers of the [analgesic] products now on the market." (Klumpp, RX 258Z001, Z040). It was Sterling's position that relaxation of the standard would allow unnecessarily substandard materials to be used (Winig, Tr. 13714; RX 218, RX 408, RX 413; complaint counsel's admission no. 527).

1097. The USP does not impose the highest standards for drug products that are technologically possible. In setting standards, the USP takes into consideration the ability of manufacturers to meet the standards (Klumpp, RX 285K). For example, in the late 1960's a proposal was submitted to the USP to raise the FSA level permitted from .15% to 1%. Eventually adopted was a standard permitting .3%. Sterling's standard at [**271**] this time, and at all times, was 0.035% free salicylic acid (Klumpp, RX 285M-O, R-S).

1098. Based on Bayer Aspirin's formulation and the manufacturing techniques and processes involved, Dr. Banker concluded that Sterling Drug, to his knowledge, has more closely optimized the 5–grain aspirin tablet than any other pharmaceutical company (Banker, Tr. 12710–11).

1099. Dr. Rhodes testified that, in his judgment, Bayer's specifications both for the drug substance, aspirin powder, and the drug product, aspirin tablets, are significantly and substantially greater than the USP standards (Rhodes, Tr. 11266–67).

1100. USP standards are evolving standards. The standards that were used in the compendia during the 1940's, for example, would be unacceptable to pharmaceutical scientists, drug companies, and regulatory bodies today. As time passes, assay procedures improve, additional impurities are recognized, and standards are upgraded in a continuing effort.

1101. In 1947 USP introduced standard for disintegration time of 30 minutes, which has since been gradually reduced to five minutes. In contrast, the Bayer standard has always been not more than 30 seconds (Winig, Tr. 11261–62; RX 151).

1102. Under the current USP disintegration standards, 6 tablets are originally tested and if more than 2 of these 6 may fail to meet the 5–minute standard, 12 additional tablets are tested. In all, 16 of the 18 tablets tested must pass the 5–minute standard. The 2 tablets

that do not pass the 5–minute standard need meet no limit on time (Danhof, Tr. 16943).

1103. Dr. Miller served as a member of the Drug Specifications Committee for Los Angeles County. His function was to analyze and evaluate pharmaceutical products being purchased by the county. Dr. Miller supplied data to the county which indicated that, "... the USP [disintegration] test was not adequate to sort out some faulty products." Therefore, Dr. Miller's examination included evaluation of the following criteria in order to determine the acceptability of the products: labeling, labeling legibility, variability, broken or cracked tablets, and disintegration testing using a modified procedure superior to USP. Thus, Dr. Miller used many of the same tests used by respondent in order to evaluate aspirin on behalf of Los Angeles County. Because of his dissatisfaction with the USP disintegration test, he devised his own test, which like Bayer's test, did not abrade the tablets (Miller, Tr. 6690–91, 6912).

1104. Dr. Miller testified that USP standards for aspirin powder and aspirin tablets are based primarily on what the **[272]** industry can produce at a reasonable cost. USP members will determine the standard largely through information supplied by the industry. Therefore, according to Dr. Miller, the USP does not have any preconceived notion as to how pure an aspirin should be, and the function of the USP in setting its standard for purity is limited to that of compiling a compendium on what the industry practices are, and making a judgment as to what the manufacturers on an industrywide basis can produce at reasonable cost (Miller, Tr. 7109–10). Dr. Miller agreed that the USP standard for FSA in aspirin tablets was relaxed in 1970 because some manufacturers were having difficulty in meeting it (Miller, Tr. 6916).

1105. There have been a number of reported instances to show that some drug products may meet USP standards, but nevertheless can pose serious problems of bioinequivalence as well as side effects (Rhodes, Tr. 11216–20, 11225–29; RX 250–Prescot, 11225–27; RX 250–Skelly, 11227–29; RX 250–Cooper). For example, in the case of digoxin, a widely used drug employed in the treatment of cardiac conditions, problems with bioinequivalence among brands meeting USP standards was so severe that fatalities resulted. Therefore, the National Center for Drug Analysis in St. Louis, Missouri presently tests each batch of digoxin in order to insure a suitable dissolution rate (Rhodes, Tr. 1127–30; RX 250–Skelly).

1106. The present USP does not contain any standard for bioavailability. According to Dr. Rhodes, the establishment of such standards is a goal of the USP (Rhodes, Tr. 11191–95; RX 284Z068).

1107. According to Dr. Banker, USP standards regulate only a very

limited number of excipients, and the standards for excipients are not currently adequate to meet the needs of the pharmaceutical industry (Banker, Tr. 12601–02).

1108. Dr. Rhodes testified that merely because a drug product is labeled as a USP product does not necessarily mean that it in fact complies with all of the applicable USP standards (Rhodes, Tr. 11136, citing Ulrich, C., "The Generic Drug Dispute in Louisiana," *J. Louisiana Med. Soc.,* 117:141 (1965); Friend, D., "Pharmaceutic Preparation and Clinical Efficacy of Drugs," *Clin. Pharm & Therap.,* 3:417 (1962); Stetler, C., "Therapeutic Equivalency of Drugs - Fact or Fiction?," *Med. Ann. D.C.,* 38:297 (1969)). The existence of laws and regulations concerning pharmaceutical quality does not insure that every manufacturer complies with such laws and regulations at all times or on all occasions (RX 413, complaint counsel's admission request no. 372).

1109. In comparing aspirin brands, it would be unrealistic and scientifically invalid to base a judgment of pharmaceutical [**273**] superiority upon any single factor. Therefore, the fact that a particular brand may have equaled or exceeded another brand on a single parameter is insufficient evidence to conclude that it is pharamaceutically or therapeutically equivalent or superior to the other brand. Aspirin brands must be evaluated in terms of all pertinent parameters bearing upon pharmaceutical quality and therapeutic efficacy (Rhodes, Tr. 11838–42; Banker, Tr. 13143–52).

1110. Furthermore, whatever pharmaceutical differences may be observed among plain 5–grain aspirin tablets, the differences must at the least be statistically and clinically significant to support a claim of comparative quality. Consumers do not have the knowledge and means of distinguishing spurious claims based on trivial or meaningless differences from claims based on significant and real quality differences which are also clinically significant.

1111. Based upon a careful review of the record as a whole, it is found that the evidence does not show that Bayer Aspirin is superior in terms of quality, purity, freshness, stability, and speed of disintegration, to all other plain 5–grain aspirin brands. The most that can be said for Bayer, without intending to suggest demonstrated pharmaceutical or therapeutic superiority of Bayer, is that Bayer appears to have an edge in terms of FSA levels and product stability among the national brands. For example, when the FDA in the mid–1970's required drug labels to show expiration dates, Bayer Children's Aspirin was the only one which was permitted a 10–year life while other brands were limited to FDA's usual 5–year period (Banker, Tr. 12593; Winig, Tr. 14289).

1112. There is also no evidence showing that Sterling, in formulating or establishing the manufacturing processes and control proce-

dures related to Bayer Aspirin, sought to implement the principle of optimization, a relatively recent concept. What the Sterling witnesses testified to was their judgment that, based on the physicochemical characteristics of a large number of aspirin samples tested by Sterling and others, Bayer Aspirin was of superior quality *overall.* The record shows that this judgment was not based on systems analysis or any other statistical optimization technique but rather upon eyeballing the comparative physicochemical data in the record. Viewing the record in terms of overall product quality, the much firmer conclusion that emerges is that Bayer is one of a number of high quality 5–grain aspirin brands available to consumers (CX 448; CX 430A-B). [**274**]

VI. THE "223 TEST" REPORT (CX 448) DOES NOT PROVIDE A REASONABLE BASIS FOR THE CLAIM THAT BAYER IS QUALITATIVELY OR THERAPEUTICALLY SUPERIOR TO ALL OTHER TESTED BRANDS

1113. As substantiation for various advertising claims under challenge in this proceeding respondent has referred to a report of a study entitled "Quality Comparison of Bayer Aspirin and Competitive Aspirin Products on the American Market," or the "223 Test," CX 448. CX 448, dated March 1971, reports the results of an in-house study comparing Bayer with 220 brands of plain 5–grain aspirin in terms of 30 pharmaceutical characteristics (CX 448, pp. I, J). The purpose of this study was to evaluate and insure Bayer's continued superiority, by surveying the United States aspirin market and comparing Bayer with competitors in terms of "quality, reliability, and elegance" (CX 48I). The study was conducted entirely by respondent's own employees, from the collection of aspirin samples, to recording sensory and laboratory observations, to writing the report. The "Blue Book" advertising campaign was in part based on this study (CX 678, admission 255). All the backup material related to CX 448 was produced to complaint counsel. Excerpts from such material in the record are CX 429 and RX 181.

1114. The identification of brands was made by Sterling's salesmen in 1967 (CX 448I; Mattimore, Tr. 15336–38). The samples were purchased in 1968 (CX 448I) by respondent's sales representatives (CX 448K; Mattimore, Tr. 15369–72). The collected samples were first examined by Dr. Marcelli (Tr. 17436–37; Mannix, Tr. 14608; CX 448O, P). The samples were next examined by the Quality Control staff at the Trenton plant for various attributes, *e.g.,* aspirin content, FSA level, disintegration (Mannix, Tr. 14608, 14610; Marcelli, Tr 17444; CX 448O). The Quality Control staff's results were partially subjected to statistical analysis performed by members of a statistical staff at the Sterling-Winthrop Research Institute (SWRI) (Marcelli, Tr. 17637–42). In 1971, Dr. Marcelli assembled and reported the test results,

including those from her own observations, those generated by the Trenton staff, and those from the statistical staff in CX 448 (Marcelli, Tr. 17388).

1115. Dr. Marcelli, a graduate industrial pharmacist at the time, was assigned to the 223 Test while working for Dr. Tainter as a Special Project Assistant for the Sterling Research Board. Dr. Marcelli had overall responsibility and supervision for all aspects of the study except the sample pickup. She was responsible for determining the attributes to be tested, conducting analysis of the data, and writing the report (Marcelli, Tr. 17401–02, 17404–05).

1116. It is respondent's position that the 223 Test was a properly conducted study and that its results are valid and reliable. Respondent contends that the study demonstrates that **[275]** Bayer Aspirin was pharmaceutically superior to other aspirin brands on the market, and that said study was, therefore, properly relied upon as a basis for claims of pharmaceutical superiority in the Blue Book campaign. Furthermore, respondent contends that, if an implied representation of therapeutic superiority is found in this case (contrary to its view), the 223 Test, in addition to other evidence, shows a reasonable basis for such representation.

1117. The samples of aspirin tested in the 223 Test were assembled as a result of a survey conducted in 1967 and a pickup of samples in 1968 (CX 448K-L; Alberts, Tr. 8952; Mattimore, Tr. 15336–38). In early 1967, the sales administration manager of respondent's Glenbrook Laboratories Division, Mr. Mattimore, was asked by his superior to conduct a survey to identify the various brands of aspirin which were available for sale in retail outlets in the United States. This was carried out by requesting every Glenbrook Laboratories salesman to report all brands of aspirin they encountered in a one-week period. The salesmen were provided with a form and instructed to record the name of every brand of 5-grain aspirin, and the name and address of the store in which it was found (Mattimore, Tr. 15336; CX 448K).

1118. Mr. Mattimore estimated that approximately 100 men went into approximately 3,350 stores, 35 per week per man. The salesmen were asked to go into units of all the major chains so that their coverage would reflect the brands in all outlets of such chains. In Mr. Mattimore's view, the survey reflected what was being sold in at least 70 or 80% of the stores in the United States at that time (Mattimore, Tr. 15336–38).

1119. In 1968, Mr. Mattimore was asked to obtain samples of the brands which had been identified in the survey. This was carried out in three stages—collection of samples of minor or regional brands, collection of samples of major brands, and collection of Bayer samples (Mattimore, Tr. 15338; CX 448K-L).

1120. In the first stage, in March 1968, the collection of samples of minor or regional brands, Mr. Mattimore assigned salesmen to pick up specific brands by going through the 1967 report forms and identifying salesmen who had reported such brands. Mr. Mattimore testified that this was the only practical way to proceed because store or private-label brands are commonly available only in particular outlets and that it was necessary to assign the task to the personnel who had located the brand initially. Otherwise, many of the brands identified the previous year would have been missed. Where a brand was clearly available in more than one location, *e.g.,* certain chain store brands, several salesmen were asked to provide samples (Mattimore, Tr. 15338–41). In the sample collection, each salesman was asked to pick up six samples of a particular brand, of different control numbers where possible (Mattimore, Tr. 15338–40). [**276**]

1121. In the second stage, salesmen were asked to pick up samples of Sterling's major competitors—Anacin, Excedrin, Bufferin, and brands which are known as nationally distributed 5–grain aspirins, including Squibb, McKesson, Norwich, and St. Joseph. Nationally distributed brands are those which are probably available in all 48 states which Sterling serviced (Mattimore, Tr. 15343). Since the objective was to get a national sample, Mr. Mattimore asked a sales representative in each of the Glenbrook 14 sales districts to obtain samples (Mattimore, Tr. 15343–44).

1122. In the third phase, Mr. Mattimore instructed salesmen to pick up samples of Bayer Aspirin, also on a national basis. This request was made to the 14 sales districts, following the same procedure as in obtaining samples of the combinations and the nationally distributed 5–grain aspirin tablets (Mattimore, Tr. 15344).

1123. When samples were received by Mr. Mattimore at his New York office, he checked them against his requests to the salesmen. Follow-ups were made if no samples were submitted for a brand, or if insufficient number of samples were received. In almost every instance, the explanation was that the representative could not locate the branded product (Mattimore, Tr. 15346). This was not surprising since there are changes in store and private-label brands (Alberts, Tr. 8953–54; Mattimore, Tr. 15348–49).

1124. The samples were generally shipped in a corrugated container, packaged with paper or some type of resilient material, sealed and shipped by mail. The Glenbrook salesmen from whom Mattimore requested samples had previous experience in picking up samples, a procedure followed with competitive products. It was Mr. Mattimore's view that in connection with the sample pick-up for this study the sales representatives did carry out his instructions properly (Mattimore, Tr. 15342–43, 15347).

1125. Mr. Mattimore testified that CX 448, pages K and L, called "Identification and Location of Brand and Acquisition of Samples," accurately describes the procedures which were followed in the 1967 survey and 1968 collection of samples (Mattimore, Tr. 15348–49).

1126. Mr. Mattimore testified that when the brand survey was conducted in 1967, and the samples were collected in 1968, neither Mr. Mattimore nor the sales representatives knew the specific purpose for which this was being done (Mattimore, Tr. 15344, 15374).

1127. In determining the characteristics to be tested in the 223 Study, Dr. Marcelli relied upon her own experience in the [277] Pharmacy Division, and also considered an earlier and less complete pharmaceutical study from the early 1960's, the results of which were available in a draft report, CX 445, "The Quality of Aspirin Tablets," by Jerome Winig and Gail Prince. On this basis, Dr. Marcelli prepared a list of characteristics which were considered important to pharmaceutical quality. The tentative list was checked with the Pharmacy Research Division of the Sterling Winthrop Division for their suggestions and confirmations. It was also discussed with Mr. Winig and Mr. Mannix at the Glenbrook Laboratories Trenton plant. Dr. Tainter approved the basic list in March 1968 (Marcelli, Tr. 17407–08).

1128. The 223 Test, CX 448, reports tests and observations of the following physical and chemical characteristics:

1. Aspirin content - USP requirements
2. Aspirin content - Bayer standard
3. Tablet weight - USP
4. Absence of capping
5. Disintegration time - USP method
6. Disintegration time - Bayer method
7. Free salicylic acid - USP limits
8. Free salicylic acid - Bayer requirements
9. Absence of off-color
10. Absence of acetic odor
11. Freedom from wicking or wadding
12. Frequency and severity of tablet miscount
13. Rate of tablet breakage
14. Clarity of package size
15. Clarity of aspirin concentration
16. Legibility of label copy
17. Presence and adequacy of indications for use
18. Adequacy and accuracy of dosage instructions
19. Presence of required caution
20. Presence of required warnings
21. Use of package insert

22. Provision of sealed package
23. Provision of safe, undamaged container
24. Presence of security-closed caps
25. Control number presence and legibility - carton
26. Control number presence and legibility - container
27. Chipping
28. Miscellaneous contents imperfections
29. Wadding presence and adequacy
30. Deficiencies in container appearance

Most of the attributes were either required under regulatory or compendial requirements or were regarded as desirable by Sterling at that time. Many of the latter were later [278] incorporated into regulatory or compendial requirements (Marcelli, Tr. 17411–12; CX 448I-J).

1129. RX 181A-E, a letter from Marcelli to Winig dated April 3, 1968, included a handwritten draft report form, including examples of the types of entries to be made on the basis of physical observation of the samples in New York and of the testing to be conducted at the quality control laboratory of the Trenton plant. RX 181 was written after consultation with Winig and Mannix. It was understood at that time that the laboratory testing was to follow the standard testing procedures used in the quality control laboratories (Winig, Tr. 13743; Mannix, Tr. 14609; Marcelli, Tr. 17409–10, 17585–88). Subsequent correspondence and discussion between Dr. Marcelli and Mr. Mannix concerned the format for presentation of results and the use of pass-fail standards (Mannix, Tr. 14621–22; Marcelli, Tr. 17409, 17585–86; RX 181F-G, K).

1130. In the 1960's and early 1970's, at the time the 223 Test was conducted (CX 448), the emphasis was on tablet disintegration rate. Today the emphasis is on dissolution rate and absorption-bioavailability (Danhof, Tr. 17067). At that time, there was no standard test for dissolution or bioavailability of aspirin tablets (Winig, Tr. 13756).

1131. CX 448P-U describes the various tests and observations carried out at the Trenton laboratory (Winig, Tr. 13739; Mannix, Tr. 14609–10; Marcelli, Tr. 17464–67; CX 448P-U).

1132. This work was done under the supervision of Mr. Edward Mannix, Director of Quality Control, at the plant. Mr. Jerome Winig, the plant manager, asked that the quality control laboratories undertake the work, at the request of the Sterling Medical Director, Dr. Tainter. As Director of Quality Control, Mr. Mannix was autonomous of the plant administration, reporting to quality control officials in the company. In the 223 Test, he was in charge of the testing. He set up the program, and participated in establishing the report format.

He assigned persons directly under his supervision to undertake the testing (Mannix, Tr. 14605–07; Winig, Tr. 14255; Marcelli, Tr. 17420–22).

1133. The test procedures used in the study were routine standard testing procedures, with which the laboratory staff were familiar. The personnel, equipment and procedures regularly used for testing chemical and pharmaceutical characteristics in the quality control laboratories were used in connection with this survey (Winig, Tr. 13738, 13743, 14261–62; Mannix, Tr. 14624–25, 14609; Marcelli, Tr. 17464–67; CX 429C).

1134. The tests conducted at the Trenton Laboratories were tablet count, color, odor, general appearance and disintegration. The tablet disintegration test was done by two different methods—the USP method and the Bayer method (Mannix, Tr. 14609–10; CX 448P-U). **[279]**

1135. The USP disintegration procedure used what is commonly termed the Vandercamp apparatus, described in the USP, using discs which move and hit the tablets as the apparatus is raised and lowered in the water medium. The Bayer basket technique involves a simple screen and stirring device and is used in the normal course of Bayer quality control. The Trenton plant's quality control staff was competent in both methods (Winig, Tr. 13740–42; Mannix, Tr. 14612–13).

1136. Analytic testing procedures in effect in the Trenton plant at the time are described in CX 429D-G, "Quality Control Specifications for Bayer Aspirin Tablets." These were the standard testing procedures used by the quality control group, and were taken from the plant monograph then in effect. They cover all the items dealt with in CX 448, except for color, odor, tablet count, and the USP disintegration method referred to above (Winig, Tr. 13742; Mannix, Tr. 14613–14; Marcelli, Tr. 17464–67).

1137. Testing began at the Trenton Laboratories for the CX 448 study in July 1968 and continued over a period of two years to August 1970 (Winig, Tr. 13737–38; Mannix, Tr. 14619; RX 181H, N-O).

1138. Two methods were used to transport the samples from Dr. Marcelli's custody in the New York office to the Trenton plant. Under one method, the samples were transported by the company's regular courier service to Secaucus, New Jersey, where there was a distribution center. There was routine transport between Trenton and Secaucus. The second method was through the mails. The mails were used when necessary (Mannix, Tr. 14628; Marcelli, Tr. 17444–46).

1139. After Mr. Mannix received the samples that were sent from Dr. Marcelli to the Trenton plant, he made assignments to various technicians to do the various tests according to their expertise and availability. The technicians were told that the work was in connec-

tion with a survey, and that they were to conduct it the same as they would an everyday procedure. No one told the technicians that the results of the study were to be used for advertising purposes. Testing of competitive products had been done previously on a routine basis (Winig, Tr. 13745; Mannix, Tr. 14622–24).

1140. At the time the testing was done, neither Mr. Winig nor Mr. Mannix had any understanding or information that the results were intended to be used for advertising purposes. It was their understanding that this was another survey of competitive products, like others that had routinely been done in the laboratories. The first information that Mr. Winig had of possible use or advertising was in the summer or fall of **[280]** 1971, at meetings to consider a new advertising campaign. Mr. Mannix was later informed of such consideration, and the resulting decision (Winig, Tr. 13736, 13752; Mannix, Tr. 14623–24).

1141. In conducting these laboratory procedures, following the usual procedures, the samples were not blinded. The purpose of the survey was to study commercial aspirin tablets in the form in which they were available to consumers, and this placed sharp limitations on blinding. Respondent's witnesses testified that since the survey employed routine, standardized tests, it was unnecessary to blind the samples and that blinding would have altered the physical composition of the tablets which is part of the evaluation (Rhodes, Tr. 11434–36, 11440–44; Banker, Tr. 12906; Fields, Tr. 16600–01).

1142. Mr. Mannix and his two supervisors were responsible for taking the data which constituted the test results from the notebooks and putting it into the reporting format to be sent to Dr. Marcelli. RX 181N-O is an example of the reporting format or reporting sheets sent from the laboratories in Trenton to the New York office (Mannix, Tr. 14625).

1143. In the collection of samples from the field, 14 Bayer samples were obtained and delivered to Dr. Marcelli. Seven of the Bayer field samples did not undergo laboratory examinations at Trenton because they were lost or destroyed in the course of transportation (Mannix, 14628–31; Marcelli, Tr. 17455–56; RX 181J; CX 429H).

1144. Efforts were made to find replacement samples for the lost Bayer samples of approximately the same age (or plant control number). These could not be found in retail establishments. Five replacements were found in Sterling facilities—four in "Free Goods 90 Park N.Y." which was a reference to aspirin which constituted part of an overshipment to a consumer or returned by a customer for credit, and one at the Sterling Winthrop Research Institute, Rensselaer. A total of 19 Bayer samples underwent physical observations in New York (Mannix, Tr. 14630; Marcelli, Tr. 17449–51).

1145. Laboratory tests were performed on the Bayer samples in August 1970. The samples tested at the laboratory were seven field samples and the five replacement samples (Mannix, Tr. 14631; Marcelli, Tr. 17454–55).

1146. In late January 1971, Dr. Marcelli undertook the analysis of the data resulting from the tests and performed the tabulation, analysis and writing of the report (CX 448). This work was done in January-March 1971. Dr. Marcelli had the advice and assistance of the Biometrics Section at the Sterling-Winthrop Research Institute, which is the expert biostatistical body at Sterling. The two handwritten tables in CX 430 were [281] prepared by the Biometrics Division. Dr. Marcelli had staff assistance in tabulating the data (Marcelli, Tr. 17478–81).

1147. Dr. Marcelli adopted a statistical cutoff for aspirin brands that were to be individually examined in the report, as the Biometrics Section indicated that comparisons should be confined to those brands where there was a minimum of six samples and at least four control lots in order to have a reasonable estimation of the distribution within the brand. All of the remaining brands were placed together in a single group labeled "Miscellaneous." At the time that this recommendation was made by the Biometrics Section, that section did not have access to any of the test results (Horner, Tr. 10762–63; Marcelli, Tr. 17482–85).

1148. It is Sterling's position that the overall conclusion arising from CX 448 is that Bayer Aspirin tablets were superior to all other plain 5–grain aspirin tablets represented in the study in terms of overall pharmaceutical quality. This was based upon analysis and evaluation of the data with respect to the 30 characteristics or categories reported on in the study. The 30 categories were divided into 26 primary categories and the 4 secondary categories. Bayer had 8 failures in 5 of the 30 performance categories, but no other brand with a reasonable representation equalled this record. The brand closest to Bayer in performance had twice as many failures. Only 3 of the Bayer failures fell into the 26 primary categories whereas with the other brands, 3 to 5 times as many failures fell into the primary categories (Marcelli, Tr. 17488; CX 448D-H; RPF 7.528).

1149. Dr. Marcelli reported that based on this 30 criteria employed in CX 448, Bayer was superior to 220 aspirin brands (CX 448D). Specifically, Bayer routinely yielded 324 mg aspirin per tablet with more lot-to-lot consistency than the other brands. One hundred fifty-seven competitors yielded at least one failure (CX 448D). For disintegration, Dr. Marcelli reported that Bayer consistently met a standard of beginning disintegration with 2 seconds and completing disintegration within 30 seconds, while 70 others failed to do so (CX 448D). For

FSA level, only one Bayer sample yielded FSA in excess of .035%, while 90% of competitive samples yielded such FSA values (CX 448E). Bayer showed a uniformly, pure white color while 9 major brands and approximately 20% of minor brands showed at least one off color sample (CX 448E).

1150. Dr. Marcelli also reported that Bayer showed perfect tablet count, but only four other major brands did so. One hundred seventy-eight minor brands showed tablet counts varying from the label claim (CX 448E, F). Bayer and 6 major brands manifested rare instances of broken tablets, while 50% of the minor brands registered broken tablets (CX 448F). Bayer and eight major brands manifested uniformly good label legibility. Most minor brands showed poor label legibility (CX 448F). On [282] packages of Bayer and five major brands, indications were clear. All minor brands registered deficiencies in the presentation of indications (CX 448F). She reported that only Bayer reliably included dosage recommendations, cautions and warnings on every sample (CX 448G). Only Bayer and St. Joseph provided package inserts (CX 448G). Among the major brands, only Bayer registered sealed units for every sample. Only a "handful" of minor brands provided such protection (CX 448G). Bayer routinely showed undamaged and safe containers, while other brands did not (CX 448G). Of the major brands, only Bayer manifested uniformly legible control numbers on cartons and bottles. Minor brands showed numerous failures, including omissions of these numbers (CX 448G). Bayer was free of extraneous dust and stray fragments, while 75% of the other brands manifested some deficiency detracting from the general appearance of the product of package (CX 448H).

1151. Dr. Marcelli concluded that Bayer alone showed failures in only 5 of the 30 categories, that those 26 parameters relating to efficacy, tolerance, stability, and safety, Bayer showed minor failures in 3 categories, and that no other brand with "reasonable representation" matched Bayer's record, and that competitive brands' failure rates ran three to five times Bayer's rate (CX 448H).

1152. Dr. Marcelli completed the report in March 1971, and distributed it to those on a list provided by Dr. Tainter. Her involvement ended with the submission of the report. Dr. Marcelli did not participate in any meetings later in 1971 that considered the report in the context of a proposed advertising campaign. She testified that she first heard of the possible use of the study for advertising purposes in late October or early November 1971, after she had left Sterling (Marcelli, Tr. 17532–33).

1153. In 1971, the 223 Test was considered by a group which included such company scientific experts as Dr. Blackmore, Director of Clinical Research at Sterling's Research Laboratory; Dr. Rosenberg,

Head of the Pharmacology Section of the Research Institute; Dr. Swarbrick, Head of the New Product Development Group and a former professor of Pharmaceutical Science (now Dean of the University of Southern California School of Pharmacy); Mr. Winig, Plant Manager at the Bayer Trenton plant and an expert in pharmaceutical and manufacturing standards in aspirin; Dr. Trout, Sterling Medical Director; and other medical personnel. A consensus was reached at those meetings that the 223 Test was valid and reliable and that it provided a basis for making a claim of superiority in pharmaceutical quality for Bayer Aspirin (Alberts, Tr. 9002–03; Winig, Tr. 13752; Trout, Tr. 16094).

1154. At the trial, respondent's expert witnesses, without exception, testified that because pharmaceutical quality is [283] related to therapeutic efficacy, physicochemical pharmaceutical tests, such as CX 448, provide a reasonable basis for conclusions regarding comparative therapeutic performance of aspirin products.

1155. Dr. Horner, respondent's expert biostatistician, testified that in assessing the clinical significance of differences in various parameters between aspirin brands, it is necessary to consider the net effect of all differences, rather than to isolate a single parameter. In this opinion, a critical issue is the assessment of overall pharmaceutical and therapeutic superiority, as opposed to making a series of independent decisions based on individual parameters (Horner, Tr. 10835).

1156. Dr. Feinstein testified that he reviewed the material in the "223 Test" (Feinstein, Tr. 16374). He described the study as containing the kind of evidence that he would resort to in making a decision as to which of the products would be better therapeutically (Feinstein, Tr. 16374, 16379).

1157. Dr. Rhodes, an expert in pharmaceutics, testified that, in his opinion, CX 448 is a valid pharmaceutical study, which demonstrates that when Bayer Aspirin was compared with a large number of other aspirin products available on the United States market, Bayer Aspirin was of better quality than those produced by its competitors. In his view, the 223 Test provides a reasonable scientific basis for the conclusion that Bayer Aspirin and Bayer Children's Aspirin have been tested against other brands of aspirin and found to be qualitatively superior to other brands. It would also be reasonable to draw a therapeutic conclusion based upon the therapeutic importance of the parameters measured in this study. In his opinion, a reasonable drug company in the late 1960's and early 1970's would have acted reasonably in selecting the parameters measured in the study in attempting to determine the pharmaceutical and therapeutic superiority of its aspirin over competitive brands of aspirin (Rhodes, Tr. 11425–26, 11434–43).

1158. It was the judgment of Dr. Banker, an expert in pharmaceutics, that the 223 Test was a comprehensive test which evaluated meaningful parameters of different brands of aspirin tablets. In Dr. Banker's view, the methodology is valid, and clearly established that Bayer was the most nearly optimized brand of aspirin tablets, and was pharmaceutically and therapeutically superior to the other brands evaluated. In his opinion, a reasonable drug company would have a right to rely on a study such as the 223 Test in making superiority claims for its aspirin and a reasonable hospital pharmacist or clinician would be justified in relying on such a study in selecting Bayer Aspirin over other brands of aspirin tablets for treatment of patients (Banker, Tr. 12779–81; Danhof, Tr. 16946–67). **[284]**

1159. Dr. Fields testified that the 223 Test was of value in selecting an aspirin brand to be used in the NIH Stroke Study because of the relationship between such characteristics and the therapeutic performance or side effects of an aspirin tablet. In the absence of controlled clinical studies, the 223 Test was considered to have a bearing upon determining which aspirin brand would produce the least variability, the most likelihood of bioavailability, and the least side effects. Among the physical and chemical characteristics considered were disintegration, amount of impurities, including free salicylic acid, and the stability of the tablet. According to Dr. Fields, the expert pharmacologists relied upon the 223 Test and other information in selecting Bayer Aspirin for use in the NIH Stroke Study (Fields, Tr. 16585–86, 16598–600, 16566, 16744–45).

1160. Dr. Scoville, a former FDA official, also testified that the 30 physical and chemical characteristics studied in the 223 Test were included in the type of material that is reviewed by the FDA, together with appropriate clinical data, in reaching judgments as to the safety and efficacy of a drug product and in determining whether to approve a drug for marketing or to seize or recall a drug product from the marketplace (Scoville, Tr. 14448–49).

1161. Dr. Falliers, an expert in allergy, testified that to the extent that the 223 Test demonstrated that Bayer Aspirin is pharmaceutically superior in the characteristics tested, it provided a reasonable basis to conclude that Bayer Aspirin is therapeutically superior (Falliers, Tr. 13320–21, 13326).

1162. The record shows that Sterling knew in August 1971, about five months after the completion of the 223 aspirin survey, that there were some 328 plain aspirin brands in the United States. Sterling knew in November 1971 that the number of competing aspirin brands was possibly as high as 442 (CX 363A; Alberts, Tr. 9045–47).

1163. The record shows that the reliability of the 223 Test and the validity of its findings are subject to serious doubts because of perva-

sive methodological deficiencies throughout the entire survey. Despite the elaborate and considerable research trappings which adorn the 223 Test, it is fair to conclude that its overall quality falls short of that generally required to substantiate unqualified claims of pharmaceutical or therapeutic superiority with respect to plain 5-grain aspirin brands. However, this does not detract anything from CX 448's utility as an ongoing internal quality monitoring tool, as its more modest predecessors had been (F. 1124, 1127, 1139, *supra*).

1164. It is well recognized that for a properly designed and well-controlled scientific study, a protocol must define in sufficient detail all of the important aspects of the study, including any plan for statistical evaluation (Moertel, Tr. [285] 6275, 6287; DeKornfeld, Tr. 8393, 8400; Horner, Tr. 10818–19, 10890–91, 10897). CX 448 does not contain any protocol (Rhodes, Tr. 11803). The draft report form contained in Dr. Marcelli's April 3, 1968 letter to Mr. Winig (RX 181A-E), although informative, cannot be characterized as a "protocol," and it does not include any description of contemplated statistical evaluation. In fact, no "protocol," in the conventional sense, was established for CX 448 (Marcelli, Tr. 17585–87). Mr. Mannix, who was responsible for overseeing the Trenton testing phase, testified that he had begun reporting test results to Dr. Marcelli before she had committed to paper what it was he was to be testing (Mannix, Tr. 14663).

1165. Test samples were collected by Sterling's field salesmen in 1968 (Mattimore, Tr. 5338–41, 15343). The record indicates that the sales representatives who collected the test samples received no written instructions concerning the manner of collection (Mattimore, Tr. 15370–79). The sales representatives simply received requests to pick up certain brands of aspirin (Mattimore, Tr. 15339). The witness called by respondent to provide evidence on the method and reliability of the collection state of this study did not remember whether or not written instructions ever existed concerning the collection of samples for major brands (Mattimore, Tr. 15374–79). No means exist to determine whether that portion of respondent's sales force involved in the collection effort had had any earlier training or experience in selecting samples (Mattimore, Tr. 15374–79) or how the sales representatives chose the retail outlets for the collected samples (Mattimore, Tr. 15378). The record does not show that any attempt was ever made to randomize any phase of the selection process.

1166. The sales representatives were not asked to report on the condition of the samples (Mattimore, Tr. 15372). They received no instructions regarding the manner of shipping the samples (Mattimore, Tr. 15372–74). Thus, no means exist to determine how much disparity there was among the samples in terms of physical appearance and storage conditions at the retail level. No way exists to deter-

mine how much disparity, if any, there was among the samples in terms of their handling after purchase and before examination in respondent's New York City office. Thus, from the very beginning, no controls were incorporated in the test for disparate condition and treatment of the samples.

1167. Mr. Mannix, who was responsible for quality control at the Trenton plant and oversaw the Trenton testing phase of the 223 Test, testified that differences in handling must be avoided to prevent biasing the results of tests, such as powdering, chipping and aspirin content, all of which were tested in the 223 Test (Mannix, Tr. 14660–61; CX 448I). Nevertheless, Sterling exercised no control over the manner of handling samples. For example, some samples were transported by special **[286]** company courier, others were transported by mail (Mannix, Tr. 14628; CX 678, admission 982). Of those transported by mail, possibly different classes were used (Winig, Tr. 14257). Some samples were handled roughly in transit and others not (Mannix, Tr. 14671–72). It made no sense to conduct tests on samples that were not collected and handled in the same way (Mannix, Tr. 14664).

1168. The 223 report itself indicates that the study failed to control for age or circumstances of handling of the collected samples (CX 448V; Rhodes, Tr. 11665–66). Without these controls, the study cannot be expected to show whether the test results (*e.g.,* tablet breakage and FSA levels) reflected differences in manufacturing practices, or age, or retail storage practices or other circumstances, of the samples (*see e.g.,* Rhodes, Tr. 1168; Banker, Tr. 13008). The former Vice President of the Glenbrook Laboratories Division and a control chemist of 42 years' experience at Sterling agreed that variables such as age, as well as conditions of storage of an aspirin product "without doubt" must be controlled as a matter both of scientific interest and with respect to the conclusions one can draw from a pharmaceutical study such as the "223 study" (Winig, Tr. 14215–56). Failure to control for such factors also can lead to biased results with respect to disintegration time and FSA levels (Winig, Tr. 14213–14). Failure to control for differences in handling can affect physical properties such as powdering, chipping or tablet weight.

1169. Dr. Marcelli selected the 30 parameters after reviewing the results of CX 445, an earlier in-house comparative study of Bayer and 152 other plain 5-grain aspirin brands (CX 678, admission 1011; CX 445A). Thus, Dr. Marcelli knew on which parameters Bayer had fared poorly or well, in comparison with other brands. She decided which parameters belonged in the primary and secondary categories (CX 448I, J; Marcelli, Tr. 17592). Dr. Marcelli placed in the primary category 10 factors which J. Winig—co-author of CX 445 (CX 445B)—characterized as matters of "pharmaceutical elegance" (CX 445H-L),

including: label legibility, adequacy of indications, adequacy of dosage instructions, adequacy of caution, adequacy of warnings, provision of sealed package, presence of securely closed caps, and presence of control number on carton and container, tablet breakage (CX 445H, I; CX 448I, J). Thus, 10 of the 16 parameters applied by Dr. Marcelli, and 10 of the 30 parameters applied in this test, comprised "pharmaceutical elegance," and not pharmaceutical quality, to a Sterling employee who for over 40 years was responsible for the manufacturing or quality control of Bayer Aspirin.

1170. The first stage of recording observations on the collected samples was conducted by Dr. Marcelli herself in respondent's New York City offices (Marcelli, Tr. 17433–35). She assessed the test samples on a "first come-first served" [287] basis (Marcelli, Tr. 17596–97). Of the 30 parameters employed in the CX 448 (CX 448I, J), Dr. Marcelli administered 16: freedom from wicking or wadding (11); clarity of package size (14); clarity of aspirin concentration (15); legibility of label copy (16); presence and adequacy of indications for use (17); adequacy and accuracy of dosage instructions (18); presence of required caution (19); presence of required warnings (20); use of package insert (21); provision of sealed package (22); provision of safe, undamaged container (23); presence of securely closed caps (24); control number presence and legibility-carton (25); control number presence and legibility-container (26); wadding presence and adequacy (29); deficiencies in container appearance (30) (CX 448I, J). All 16 criteria involved assessments by visual examination, not laboratory tests (Rhodes, Tr. 11800–01; Winig, Tr. 14255; Marcelli, Tr. 17597–99). Thus, over half of the test data resulted from sensory tests conducted by an unblinded employee of respondent, in a nonrandomized manner. None of her observations were checked or replicated by anyone else (Marcelli, Tr. 17604). Thus, this study failed to control human error for over half the test.

1171. CX 448's remaining 14 parameters were tested by members of Trenton plant's quality control staff (Mannix, Tr. 14610; 14644–48; 14651–52; 14655–57; 14659). Of the 14, 7 involved 5 separate laboratory analyses(*i.e.,* aspirin content, disintegration by the official test method, disintegration by the Bayer test method, FSA, and tablet weight) (Rhodes, Tr. 11800; Mannix, Tr. 14655–57; CX 429E-G). The remaining seven(*i.e.,* absence of capping, off color, acetic odor, tablet miscounts, tablet breakage, chipping, and miscellaneous contents imperfections) involved sensory tests (Rhodes, Tr. 11800–01; Mannix, Tr. 14646–68; CX 429D). Thus, for 23 of the 30 criteria, or over two-thirds of the test, the data were obtained from sensory tests. Furthermore, these tests were conducted by unblinded employees of respondent (Wining, Tr. 14260; CX 678, admission 988), even though blinding was

possible for at least some of the laboratory analyses (Winig, Tr. 14260–61). Thus, all personnel conducting the examinations and analyzing the test results knew the identity of the samples. Additionally, these tests were not performed in a randomized order (Winig, Tr. 13738; Mannix, Tr. 14622). Therefore, this stage of the study failed to control for human error for the remaining half of the test.

1172. Reports of the test results generated by the Trenton staff were submitted by Mr. Mannix to Dr. Marcelli on an ongoing basis (Mannix, Tr. 14662; Marcelli, Tr. 17606). The first such report, dated October 15, 1968, shows that the Trenton staff had begun conducting and reporting test results on competitive 5-grain aspirin samples before final agreement was reached on the totality of test parameters (RX 181A, F, G; K; Mannix, Tr. 14663; Marcelli, Tr. 17585–87). This, in addition to the lack of a formal protocol, increases the likelihood that the Trenton [288] tests were not conducted uniformly or in a standardized manner on all the tested samples. Without such standardization, the study failed to control for unequal treatment and inadvertent error by the testers.

1173. Mr. Mannix submitted 17 reports of Trenton test results to Dr. Marcelli (Marcelli, Tr. 17613). Dr. Marcelli had received 14 of these reports before she sent the 12 Bayer samples for testing at Trenton (Marcelli, Tr. 17605–13; RX 181J). After receiving some of Trenton's test results on competitive 5–grain aspirin samples, Dr. Marcelli stated: "[A]t least there is some encouragement in these early results to suggest that it will be possible to show differences between brands—especially between ours and others." (Mannix, Tr. 14688; RX 181K). Thus, the employee who later analyzed the data and prepared the report actually knew some test results during the course of the test. Also, she expressed an expectation that the test would show differences between Bayer and other aspirin brands. Such advance notice of partial test results and such an early expectation regarding the desired outcome of the study introduce a distinct likelihood of bias influencing the test results (Moertel, Tr. 6346; Banker, Tr. 12918–19).

1174. The 12 Bayer samples analyzed at Trenton (Mannix, Tr. 14628–30; Marcelli, Tr. 17605) were specially packed by Dr. Marcelli and sent by company courier, unlike the competing aspirin samples (Mannix, Tr. 14672–73). All or most competitive samples apparently were mailed (Mannix, Tr. 14673; Winig, Tr. 14257). Some samples sent by mail were handled roughly (Mannix, Tr. 14671). Thus, the test samples were not treated in a standardized manner and were subjected to different handling, with Bayer samples handled most carefully. Such differences in handling strengthens the possibility that the test results were, with respect to physical tablet characteristics such as

powdering, chipping and aspirin content, as likely due to chance, or a systematic bias, as to actual differences in the tested samples.

1175. Five of the 12 Bayer samples analyzed at Trenton (Mannix, Tr. 14628–30; Marcelli, Tr. 17605) came from "free goods," *i.e.*, samples returned to respondent, and thus they did not represent Bayer samples as found on the store shelves (Mannix, Tr. 14668–70; Marcelli, Tr. 17450, 17628, 17634–36). These five were not retained samples which respondent's witness Dr. Rhodes, stated would have been appropriate replacements (Rhodes, Tr. 11438–40). Thus, unlike the other brands, about 50% of the Bayer samples, which were analyzed on all parameters applied by the Trenton laboratory tests and subsequently compared to other brands, were not commercially available samples in the usual sense (Rhodes, Tr. 11803–04; Marcelli, Tr. 17450). Furthermore, despite Sterling's recognition that a range of lots and samples are necessary to draw conclusions about manufacturers (Marcelli, Tr. 17443), the range of lots **[289]** and samples represented in the 223 study were unequal. Of the major brands, Bayer was represented by 12 samples, 12 lots; Lilly by 6 samples, 4 lots; McKesson by 35 samples, 21 lots; Norwich by 36 samples, 29 lots; Rexall by 12 samples, 3 lots; St. Joseph by 43 samples, 35 lots; Squibb by 40 samples, 30 lots; Upjohn by 4 samples, 3 lots; and Walgreen's by 12 samples, 6 lots (CX 448XZ013–25; Marcelli, Tr. 17631–33). This may explain the fact that the eight other brands generated information about intra-lot variability while Bayer did not. Thus, the study provides relatively more information about at least four other major brands, *i.e.*, McKesson, Norwich, St. Joseph, and Squibb, than about Bayer.

1176. The Trenton plant staff measured FSA and disintegration, each against two limits (CX 448I). For each of the two factors, one was Bayer's internal standard employed in the production of Bayer (CX 448I). These two in-house specifications have remained constant since at least the early 60's (Winig, Tr. 14227, 14232; Mannix, Tr. 14603; 14675). The Trenton staff routinely applied these two limits in its ongoing quality control work (Mannix, Tr. 14609–10, 14675). However, in 14 of the 17 Trenton reports, the staff nevertheless employed two limits which had never been used as internal limits (Mannix, Tr. 14678; Marcelli, Tr. 17605–13). Such an error about respondent's own standards calls the reliability of this test into question.

1177. Despite the importance of setting forth the plan for statistical analysis in advance (DeKornfeld, Tr. 8400), the plans for statistical evaluation of the 223 Test data were not described in advance (Marcelli, Tr. 17637–79). Decisions to exclude certain brands from statistical analyses were made after the test results became available (Marcelli, Tr. 17482, 17637–79). One such rule was to exclude, from brand-to-

brand comparisons, several minor brands which appeared to Dr. Marcelli simply to be different bottles of the same brand, *i.e.,* they showed similar looking bottles, caps, and labels (Marcelli, Tr. 17440, 17518–25). The rationale for this decision was that the number of physical packaging similarities indicated that the *manufacturer* of the aspirin tablets was the same, and that these different labels represented only one brand (CX 48Z041; Marcelli, Tr. 17642–43). However, another equally plausible explanation, based on common industry practice, is that one repackager packaged aspirin tablets from different suppliers into similar bottles with similar caps (*see,e.g.,* Marcelli, Tr. 17644–65; Rhodes, Tr. 11371). The investigators did not, and could not, determine which explanation was correct (Marcelli, Tr. 17645), yet chose to exclude the performance ratings of several aspirin brands (CX 448Z041–Z045). The effect of grouping these brands into one "score" was to nullify the individual, good ratings of the different brands along individual parameters (Marcelli, Tr. 17719). **[290]**

1178. Another rule adopted after the tests was to exclude, from a brand-to-brand comparison, several minor brands which were represented by fewer than six samples from four lots (CX 448Z077; Marcelli, Tr. 17483, 17637–41). The rationale was that such representation was insufficient for permitting a reasonable estimate of brand performance (CX 448Z027; Marcelli, Tr. 17443, 17483). Dr. Horner, respondent's expert witness, testified that this decision was justified under the circumstances and reflected accepted statistical procedures (Horner, Tr. 10807–09, 10894–97). However, this rule (statistical cut-off point) was not applied to major brands. Both Rexall and Upjohn were represented by three lots, and yet subjected to statistical evaluation, including tests for statistical significance in comparison with Bayer (CX 448Z001–Z002, Z004; Marcelli, Tr. 17642).

1179. Apart from the considerable and extensive methodological problems discussed above, the 223 Test results do not show Bayer is significantly superior to all other tested brands in the tested respects. Six brands (McKesson, Norwich, Rexall, St. Joseph, Upjohn, and Squibb) began and completed disintegration at rates which were statistically insignificantly different from that for Bayer (F. 633, *supra*). Since the investigators failed to test for statistical significance of the brands' aspirin content averages, this survey does not show that Bayer was statistically significantly superior to all other brands in terms of aspirin content (F. 677, *supra*). It also does not show that Bayer more consistently yielded 100% of label claim than all other tested ASA brands (F. 677, *supra*). Since the investigators similarly failed to test FSA level data for statistical significance, this survey does not show that Bayer yielded a statistically significantly lower

FSA level than all other tested brands (F. 733, *supra*). The 223 Test did not include dissolution or blood level tests.

1180. Thus, several significant methodological deficiencies occurred throughout the stages of the "223 Test." These deficiencies cannot be brushed aside. They raise a distinct possibility that the test results were as likely due to chance, or a systematic bias, as to actual differences in the tested brands. This possibility leaves the validity and utility of the test data in question. Even if these problems were disregarded, the test data discussed in F. 1179, *supra,* alone show that this test did not demonstrate that Bayer was pharmaceutically or qualitatively superior to all the other 220 tested brands in the designated respects.

1181. Since the "223 Test" is not a clinical test, conforming to accepted scientific guidelines for a well-controlled clinical trial, it cannot offer any reliable conclusion regarding the therapeutic performance of the tested brands. It purported to assess various brands of plain 5-grain aspirin only in terms of pharmaceutical characteristics. **[291]** Although respondent's expert witnesses testified that the 223 Test (CX 448) is sufficient basis for reaching a clinical judgment that Bayer is superior overall to other brands, the record as a whole is clear that none of these pharmaceutical characteristics has been shown to relate, directly and reliably, to comparative therapeutic performance of aspirin.

1182. In addition, the medical director for Glenbrook Laboratories from 1971–1974 believed it very unlikely that therapeutic differences could be shown between two brands, both passing parameters (aspirin content-USP), 3 (tablet content-USP), and 7 (FSA limit-USP) (CX 448I) (John, Tr. 5564). Furthermore, the record as a whole shows that the scientific community has not recognized tests of such physicochemical properties, as were tested in CX 448, as providing anything more than a hypothesis concerning possible clinical effects (Grossman, Tr. 7499–7500). The hypothesis must be subjected to clinical testing, and the hypothesis alone provides no evidence of clinical or therapeutic superiority (Grossman, Tr. 7499–7500; DeKornfeld, Tr. 8414–17; Moertel, Tr. 6308–09).

1183. Dr. Marcelli stated that a brand with superior ratings for eight factors (for FSA, color, odor, wicking or wadding, aspirin content, capping, breakage, and disintegration), would likely be therapeutically superior to other brands (Marcelli, Tr. 17670–82). Applying this standard to the reported results of the "223 Test," Parke-Davis, Acme, and Tripple AAA would be likely to be therapeutically superior to Bayer (Marcelli, Tr. 17670–82; CX 430A-B).

1184. Therefore, the 223 Aspirin Test is not sufficient to substantiate the representation, as alleged in Complaint Paragraph Twenty,

that Bayer Aspirin is qualitatively superior in the designated respects, including speed of disintegration, to all other aspirins tested. Moreover, the 223 Test is not sufficient to substantiate the representation, as alleged in Complaint Paragraph Twenty, that Bayer is therapeutically superior to all other brands because at the time of this representation a substantial question existed, as recognized by experts qualified by scientific training and experience to evaluate the safety and efficacy of OTC analgesic agents, concerning the validity, significance and application of such tests to the question of therapeutic superiority.

1185. Respondent has also offered, as Bayer advertising substantiation, certain reports of recalls of brands of plain 5–grain aspirin published by the FDA (RX 152 for identification; *see, e.g.,* Banker, Tr. 12581–82). Such recalls have been undertaken voluntarily by manufacturers (Miller, Tr. 6941–42). Many of the recalls occurred because of violations of the GMP (Miller, Tr. 6945–48, 6950, 6956). These violations typically involved deficiencies in a manufacturing or distribution facility, rather than with the recalled products (Miller, Tr. [**292**] 6941–42, 7104). The record indicates that these recalls neither constituted a widespread problem (*see, e.g.,* Banker, Tr. 19582), nor involved major aspirin manufacturers, *e.g.,* St. Joseph, Squibb, Rexall, McKesson, and Norwich (Miller, Tr. 7105; Banker, Tr. 12930). Therefore, the history of recalls reported in this record does not provide a reliable basis for predicting the comparative therapeutic performance of plain 5–grain aspirin brands.

1186. Respondent has also offered, as Bayer advertising substantiation, certain reports of complaints by commercial institutional customers about various pharmaceutical attributes of some competitors' aspirin. The first, RX 215, consists of complaints to Monsanto, a major manufacturer and supplier of aspirin powder (Rhodes, Tr. 11336–43). The second, RX 217, consists of complaints to Norwich-Eaton, a manufacturer of aspirin tablets (Rhodes, Tr. 11347–70). Respondent acquired this material after 1974 (Tr. 8821–32). This record does not indicate that these complaints resulted in therapeutic problems to consumers. This record does not cite complaints to other major aspirin manufacturers or distributors, *e.g.,* St. Joseph, McKesson, Squibb, Dow (*see, e.g.,* RX 215). No witness pointed to information concerning the duration of the complaints (*see, e.g.,* Banker, Tr. 12987). In addition, this material contains notes and several pages of handwriting (Banker, Tr. 12987, 12992). Dr. Banker, respondent's witness, stated he was unable to vouch for the accuracy or precision of the information presented in RX 217 (Banker, Tr. 12992). Therefore, these reports do not provide a reliable basis for predicting the comparative therapeutic performance of plain 5–grain aspirin brands.

1187. Respondent has also offered, as Bayer advertising substantiation, materials concerning manufacturing specifications used by various aspirin manufacturers and tabletters, including respondent. They include RX 205, Dow's specifications for aspirin powder (Rhodes, Tr. 11327); RX 214, Monsanto's standards for supplying aspirin powder to various tabletters, *e.g.,* Bristol-Myers, Upjohn (Rhodes, Tr. 11332); and RX 169–170, respondent's specifications (Rhodes, Tr. 11305–08). These specifications typically present internal standards for pharmaceutical attributes, *e.g.,* FSA level, aspirin content, and for various stages in the formulation and tabletting of aspirin (*see, e.g.,* RX 214A, RX 169, respectively). Although aspirin manufacturing process and quality control clearly related to pharmaceutical quality of the finished product, the record does not show a direct and reliable correlation between these manufacturing standards and aspirin's clinical performance.

1188. No witness pointed to information concerning the effective period of the specifications or their completeness. This material does not include specifications for St. Joseph, Rexall, and McKesson (Banker, Tr. 12889, 13167). Moreover, no [**293**] witness for respondent had reviewed specifications for all of the approximately 100 aspirin manufacturers (*see, e.g.,* Banker, Tr. 12615, 12887–90; Rhodes, Tr. 11716–18). Therefore, these manufacturing specifications fail to provide a reliable basis for predicting comparative therapeutic performance of plain 5-grain aspirin brands.

1189. The combining of results from multiple tests into one composite "score" or "pooling" is scientifically appropriate only under certain conditions: (1) when plans to pool tests' results have been set forth in advance in the respective tests' protocols (Rickels, Tr. 8062–64); (2) when each test has been conducted according to the same protocol (Rickels, Tr. 8062–64); and (3) when each test has been sufficiently controlled to yield reliable results (*see, e.g.,* Banker, Tr. 12904).

1190. The various tests reviewed and discussed in this record do not meet these criteria. Very few of these tests included protocols. Those with protocols did not contemplate pooling, and those with protocols did not follow the same protocol.

1191. The record shows that none of the pharmaceutical studies respondent relies on were sufficiently controlled to yield reliable results. Many involved inadequate sampling or inadequate information to determine the adequacy of sampling. Respondent's expert witnesses have stated that representation by less than 10 samples is inadequate (Rhodes, Tr. 11478), representation by one lot is inadequate (Banker, Tr. 13145), and that variables which can affect the property under investigation, *e.g.,* age as it affects FSA level and aspirin content, must be ruled out or controlled (Banker, Tr. 12904).

1192. More importantly, before differences in any test data can be attributed to real differences in test samples (rather than chance), appropriate statistical evaluation must show that the differences were statistically significant. Most of the tests failed to include statistical evaluation and those which did generally lacked sufficient controls. Therefore, the tests discussed in this record do not meet the criteria for pooling and no composite score based on pooling can provide any scientific basis for a comparative pharameutical or therapeutic conclusion regarding different brands of plain 5–grain aspirin tablets.

1193. Hundreds of brands of adult plain 5–grain aspirin were commercially available during most, if not all, the time period of 1969–1974. In a September 22, 1971 memorandum, J. C. Marshall reported the identification of 422 different brands as of November 1971 (CX 363A).

1194. Therefore, at the time of the representation alleged in Complaint Paragraph Ten A, Sterling did not have a [**294**] reasonable basis for making the representation that Bayer is superior in terms of significant therapeutic effect to any other aspirin, because respondent lacked competent and reliable scientific evidence sufficient to support this representation.

VII. ARTICLES INCLUDED IN AND TESTIMONY BASED ON RX 250 FOR IDENTIFICATION DO NOT PROVIDE A REASONABLE BASIS FOR CHALLENGED ADVERTISING CLAIMS

A. *Legal Standard*

1195. During the trial, as part of its attempt to show a reasonable basis for certain challenged advertising claims, Sterling cited a large number of scientific articles and other textual material, collectively marked RX 250 for identification, as substantiation of these claims, and relied on testimony from its witness with respect to these articles. In order for these articles and the testimony elicited about them to constitute substantiation, there must be some showing that Sterling both possessed and relied upon these articles at the time it disseminated the challenged advertising claims. *Pfizer, Inc.*, 81 F.T.C. 23, 64–67 (1972).

B. *Possession*

1196. Dr. George Goldstein, medical director of Sterling from 1975 to the present, was respondent's sole witness with respect to possession of the RX 250 for identification materials. Because he was not employed by Sterling prior to 1975 (RX 274A-B), he could not testify regarding whether Sterling possessed any of these materials when

these claims were being made by drawing inferences from certain other facts either from his personal knowledge or by drawing appropriate inferences from other facts known to him during that period.

1197. Dr. Goldstein attempted to show possession of 19 of the RX 250 articles listed in Table I (CPF 452–453) solely by inference from the fact that they were turned over to the FTC pursuant to a 1971 subpoena. This may show that Sterling physically possessed these articles at the time they were produced to the FTC in 1971, but there is no evidence in the record to indicate that they possessed them *prior to* that time. Therefore, respondent has failed to carry the burden of proof of showing that these articles were possessed by it at the time it made the challenged advertising claims disseminated prior to 1971.

1198. Dr. Goldstein attempted to show Sterling's possession of 71 of the RX 250 articles listed in Table II (CPF 454–458), by inference derived solely from the fact that for each article another article from a different edition of the same journal in which it appeared had been turned over to the FTC pursuant to 1973, 1971 or 1966 subpoenas. From this Sterling would infer **[295]** that it was a regular subscriber to these journals and therefore possessed these articles at the time of the dissemination of the challenged advertisements. There is no evidence in the record, however, that Sterling subscribed to or regularly received these journals or that any corporate official or others responsible for preparation, review or approval of the advertising claims in question read them or relied on what he read with respect to any advertising claim. Indeed, Sterling has maintained that it has not made any of the advertising claims alleged in the Complaint. In these circumstances, Sterling has failed to carry the burden of proof of showing that these articles were possessed by and relied on it at the time it made the challenged advertising claims.

1199. Dr. Goldstein attempted to show possession of nine RX 250 articles listed in Table III (CPF 459) by inference derived solely from the fact that these articles had been turned over to the FTC pursuant to a subpoena or demand not otherwise identified in the record. There is no evidence in the record to indicate the year of the subpoena or subpoenas in response to which any of the nine articles was produced. Accordingly, there is no evidence in the record to indicate *when* Sterling possessed these articles. Thus, respondent has failed to carry the burden of proof of showing that it possessed these articles at the time it made the challenged claims to which these articles may relate.

C. *Reliance*

1200. Dr. Goldstein attempted to show Sterling's reliance on 19 of the RX 250 articles listed in Table IV (CPF at 460–461), solely by inference from the fact that these articles had been turned over to the

FTC pursuant to a 1971 subpoena. Dr. Goldstein accordingly left to inference that the articles were supplied for the same purpose in 1971 as at trial, an inference for which there is no evidence in the record. There is no evidence in the record to indicate for what purpose they were produced to the FTC in 1971. Sterling has failed to carry the burden of showing that these articles were relied on by it for substantiation of the challenged claims at the time of their dissemination.

1201. Dr. Goldstein attempted to show Sterling's reliance on 12 of the RX 250 articles listed in Table V (CPF at 462), solely by inference from the fact that these articles had been turned over to the FTC pursuant to a 1966 subpoena. Dr. Goldstein accordingly left to inference that the articles were supplied for the same purpose in 1971 as at trial, for which there is no evidence in the record. There is no evidence in the record to indicate for what purpose they were produced to the FTC in 1966. Sterling has then failed to carry the burden of showing that these articles were relied on by it for substantiation of the challenged advertising claims at the time of their dissemination. **[296]**

1202. Dr. Goldstein attempted to provide reliance on 71 of the RX 250 articles listed in Table VI (CPF at 463–467), solely by inference from the fact that for each article another article from a different edition of the same journal in which it appeared had been turned over to the FTC pursuant to 1973, 1971, or 1966 subpoenas. Dr. Goldstein testified that since the literature of interest to the medical staff at Sterling is too voluminous to keep abreast of, the Sterling library staff digests pertinent articles (Goldstein, Tr. 14778–80). His testimony left to inference the following: that Sterling subscribed to or regularly received these journals; that these journals were regularly received by Sterling's library staff; that these journals were regularly digested by Sterling's library staff; that the criteria which Sterling's library staff used in determining which articles should be digested encompassed each of these articles; that these articles were digested accurately, correctly, and adequately; that these digests came to the attention of the appropriate person on Sterling's medical staff; that this person read and understood these digests; that (s)he was sufficiently interested in the articles after reading the digests to request copies of these articles from the library; that this person received, read and understood these articles; and that this person relied on the information in these articles to substantiate the challenged claims. There is no evidence in the record to support any of these inferences. Respondent has thus failed to carry the burden of proof of showing that they relied on these articles at the time it made the challenged claims.

1203. Dr. Goldstein attempted to show that 16 of the RX 250 arti-

cles, listed in Table VII (CPF at 468–469), substantiate challenged claims. All of these articles were published after 1964, postdating the period when the challenged claims were made. There is no evidence in the record to indicate that respondent possessed or had knowledge of these articles prior to their publication date. Therefore, Sterling has failed to carry the burden of showing that it possessed and relied on this material for substantiation of the challenged claims at or prior to the time of their dissemination.

1204. Dr. Goldstein attempted to show Sterling possessed and relied upon 49 of the RX 250 articles, all published from 1970 to 1974, and list set forth in Table VIII (CPF at 470–473). There is no evidence in the record, nor any inference suggested, to indicate that Sterling possessed or had knowledge of any of these articles prior to their publication. Therefore, Sterling could not have possessed and relied on these articles to substantiate challenged claims that were disseminated prior to their publication date (CX 630–634).

1205. Dr. Goldstein attempted to show Sterling possessed and relief on RX 250-Wood solely by inference from the fact that [**297**] this paper was presented prior to its publication at a meeting of the American Pharmaceutical Association in New York in 1964 (G. Goldstein, Tr. 14940–41). This evidence relies on the following inferences: that a Sterling representative was present at this presentation; that complete and accurate copies of the unpublished RX 250-Wood were available; that a Sterling employee obtained a copy of RX 250-Wood at the presentation; that this employee brought the paper to the attention of the appropriate person on Sterling's medical staff; that this medical staff person read and understood the paper; that this person would have relied on this paper to substantiate challenged claims at the time of their dissemination; and that the paper presented at the APHA meeting was identical to RX 250-Wood in all material respects. There is no evidence inthe record to support any of these inferences. Respondent has thus failed to carry the burden of proof of showing it possessed and relied upon this article at the time it made the challenged claims.

1206. Dr. Goldstein attempted to show that Sterling possessed and relied upon three of the RX 250 articles listed in Table IX (CPF at 474), by inference from the fact that they are currently in Sterling's library. This evidence relies on the following inferences: that this article was in Sterling's possession at the time the challenged claims were disseminated; that the journals they appeared in were regularly reviewed by Sterling's library staff; that these journals were regularly digested by the library staff; that the criteria which Sterling's library staff used in determining which articles should be digested included each of these articles; that these articles were digested correctly and

adequately; that these digests would have come to the attention of the appropriate person on Sterling's medical staff; that this person would have read and understood these digests; that this person would have been sufficiently interested in the articles after reading the digests to request a copy of these articles from the library; that this person would have received these articles; that this person would have read and understood these articles; and that this person would have relied on the information in these articles to substantiate the challenged claims. There is no evidence in the record to support any of these inferences. Respondent has thus failed to carry the burden of proof of showing that it possessed and relied on these articles at the time it made the challenged claims.

1207. Dr. Goldstein attempted to show reliance on nine RX 250 articles, listed in Table X (CPF at 475), by inference from the fact that the articles were turned over to the FTC pursuant to a subpoena request. There is no indication in the record as to the year of the subpoena request pursuant to which each was produced. Dr. Goldstein left to inference that the articles were supplied for the same purpose in the subpoenas as at trial, [298] for which there is no evidence in the record. There is no evidence in the record to indicate for what purpose they were produced to the FTC. Sterling has thus failed to carry the burden of showing that these articles were relied on by it for substantiation of challenged claims at the time of their dissemination.

D. *Testimony of Witnesses Contacted by Sterling After Dissemination of Challenged Claims Do Not Provide a Reasonable Basis for Such Claims*

1208. In order for the expert opinion testimony adduced at trial to be relied upon by Sterling as providing a reasonable basis for advertising claims, such opinion must have been possessed and relied upon by Sterling at the time of dissemination of the challenged claims. *Pfizer, Inc.*, 81 F.T.C. 23, 67, 71 (1972).

1209. Sterling offered no evidence that Drs. Horner, Rhodes, Banker, Stander, Scoville, Fields, Feinstein, and G. Goldstein, were contacted by it prior to the commencement of this proceeding, and the opinion testimony cannot be relied upon by Sterling now to show reasonable basis for any of the challenged advertising claims involved in this proceeding.

VIII. SECTION 5 LIABILITY FOR DISSEMINATION OF "INCONSISTENT" ADVERTISING CLAIMS REGARDING DIFFERENT DRUG PRODUCTS

1210. As found hereinabove (F. 398–402, *supra*), Sterling made

contemporaneous and inconsistent advertising claims with respect to Bayer Aspirin, Vanquish and Cope.

1211. Complaint Counsel urge that contemporaneous dissemination by an advertiser of "inconsistent" performance claims for different OTC internal analgesic drug products is unreasonable and unfair and constitutes an unfair trade practice within the meaning of Section 5 of the FTC Act (CB at 110–116).

1212. Complaint counsel's theory of Section 5 liability would introduce a new legal requirement of "consistency" in advertising regulation. It would go beyond determining whether an advertising claim regarding a product is false or deceptive or otherwise unfair to consumers and place upon an advertiser the requirement that its advertising claims for different products it markets at a given time be consistent with each other. Complaint counsel have not spelled out the content of this new requirement, except to argue generally that, by definition, mutually inconsistent claims cannot be both true at the same time. Complaint counsel have not pointed to any authority for their view. It is the administrative law judge's view that such a requirement will have a chilling effect on [**299**] protected commercial speech by effectively placing every multiproduct advertiser at peril to take care that its advertising claims for all its products at any given time not be "inconsistent" although each claim may be based on a reasonable basis.

IX. CORRECTIVE ADVERTISING WITH RESPECT TO BAYER IS NOT WARRANTED

A. *There is Substantial Evidence Showing That a Significant Portion of Consumers Held Superior Efficacy/Safety Image for Bayer Aspirin From 1967 Through 1975*

1. Image and Advertising Penetration Studies

1213. An advertising penetration study measures the level and content of what consumers recall from past advertisements for a brand (Ross, Tr. 5802–03). Unlike a copy test which tests the consumer's recall of a specific advertisement immediately after or within a day of his or her exposure to it, a penetration study tests the consumer's recollection of advertisements for some period of time past, in terms of either the recent past or a specified number of months past (Ross, Tr. 5804). A penetration study accordingly reflects advertising themes from a variety of advertisements that may have been disseminated over some period of time prior to the measurement (Ross. Tr. 5804). On the other hand, an image study is aimed at measuring the level and content of consumer images of a particular brand or brands apart from advertising recall as such. To this extent, image

studies provide more direct and meaningful information regarding a brand's image than do penetration studies, which focus on consumer recall of advertising themes and can indirectly shed light on brand images as related to past advertising campaigns.

1214. There are three so-called image studies in the record: (1) CX 395, the Assets and Liabilities Study of Adult Analgesics ("Assets and Liabilities") by Dancer-Fitzgerald-Sample, Inc., dated December 1, 1967; (2) CX 404, A Study of Vanquish's Market Opportunities ("Vanquish Study"), by Benton & Bowles, Inc., November 1979; and (3) CX 521, the Consumer's view of the Relative Effectiveness of Various Brands of Aspirin ("The Zeisel Image Study") by Hans Zeisel, 1975 (Joint Hearings Tr. 426, 2055; Zeisel, Tr. 4742). The Assets and Liabilities Study and the Vanquish Study were done for commercial purposes by advertising agencies (CX 395, CX 404; Miller, Joint Hearings Tr. 209–10; Pernica, Joint Hearings Tr. 1891). The Zeisel Image Study was conducted at the request of complaint counsel for this proceeding (Zeisel, Tr. 4649–50).

1215. A brand image is a group of general impressions that people hold about a particular brand. It is the personality or [**300**] character of a brand (Miles, Tr. 9355; Haley, Tr. 10567, 10605–10; Lipstein, Tr. 12228).

1216. There are multiple factors that are involved in brand imagery: favorable or unfavorable experience with the brand word-of-mouth; nonverbal communication, such as the package, graphics, name, or price; favorable or unfavorable publicity; sheer longevity and visibility in the market; the amount of advertising regardless of content; advertising content; product innovation; store displays; promotional activities, and other sources. A brand image is not a direct reflection of advertising (Miles, Tr. 9355–59; Haley, Tr. 10567, 10605–10; Lipstein, Tr. 12037).

1217. Brand images are formed in different ways, both within and across product categories. For example, the image of a product that has recently been introduced into the market would stem more from advertising and positioning. The longer a brand is in existence the less its image stems from the content of advertising and, particularly, from the content of a specific advertising campaign (Miles, Tr. 9355–56, 9366; Haley, Tr. 15069).

1218. There are a number of cues that relate to the overall evaluation of a product as an excellent product, some of which come from the product itself, from price, from the label, from the length of time it has been on the market (Haley, Tr. 10670).

1219. The role of advertising in the formation of brand images varies according to the age of the brand. Newer products have images that are more malleable; for longer term brands, the images are

formed early and subsequent to that the role of advertising is primarily to remind consumers of the brand's existence (Haley, Tr. 10569, 10651).

1220. Brand imagery comes substantially from advertising for those brands where the advertising theme is the brand's reason for being and that theme is consistently advertised year after year. For example, Excedrin's reason for being was that it was an "extra strength" pain reliever, different from plain aspirin. This advertising claim was used consistently over time and as a consequence, advertising contributed heavily to its extra strength image (Miles, Tr. 9356).

1221. For an old established brand, such as Bayer, brand familiarity is the primary influence: predominance in stores, word-of-mouth, and length of time on the market are all very important. Advertising maintains the brand's salience but has little influence on the image (Haley, Tr. 10651).

1222. It is recognized that there are several basic principles in interpreting consumer research, including image research, which must be taken into account. **[301]**

1223. One of the fundamental principles that has been confirmed by studies over decades is that consumers will generally rate an advertised brand higher than an unadvertised brand. The fact of television advertising visibility indicates to the consumer that the brand is a well-known brand. The absence of advertising indicates the opposite. Thus, advertising produces a substantial effect on ratings in an image study whether or not people can remember any specific sales points from the nationally advertised brand (Miles, Tr. 9396–97).

1224. Complaint counsel's expert, Dr. Ross, acknowledged the principle that consumers will rate advertised brands better than nonadvertised brands and noted that there are studies that confirm it (Ross, Tr. 5863–64).

1225. Consumers generally tend to rate advertised brands higher than unadvertised brands on desirable product attributes, whether or not the attribute had been advertised or not advertised by the particular brand (Miles, Tr. 9389). This propensity is particularly pronounced with respect to generic attributes, such as being an effective or generally good pain reliever in case of an analgesic product.

1226. National brands are more highly regarded than non-national brands or store's own brands. Consequently, consumers will tend to rate national brands higher than store's own brands or unadvertised brands on most attributes (Ross, Tr. 5863–64; Miles, Tr. 9389; Amstutz, Tr. 10100–07; Haley, Tr. 10577–80, 10585; Lipstein, Tr. 12032).

1227. In a chapter written by Dr. Ross, "Applications of Consumer Information to Public Policy Decisions," contained in Scheth and Wright, *Marketing Analysis for Societal Problems,* Dr. Ross describes

"surrogate indicators of quality" and the first one listed is that nationally advertised brands are considered to be of higher quality than store brands (Ross, Tr. 5863–64).

1228. Users of a brand generally tend to rate their brand higher than nonusers of a brand (Ross, Tr. 5862–63; Miles, Tr. 9389, 9405; Amstutz, Tr. 10125; Haley, Tr. 10585; Lipstein, Tr. 12031).

1229. There is a high relationship between familiarity and awareness of a brand and high ratings of that brand (Haley, Tr. 10585, 10604; Lipstein, Tr. 12030).

1230. In viewing the image data in evidence, it is important to take into account the influence of Bayer's long-term position in the market. **[302]**

1231. Bayer Aspirin's brand image is in the entire analgesic market and not just in relation to all other 5–grain aspirin (Miles, Tr. 9360; Haley, Tr. 15076–78; Lipstein, Tr. 12028–29).

1232. The history of the analgesic market must be taken into account because it is an important factor in brand imagery. Bayer Aspirin was invented around the turn of the century and for years had the exclusive right to use the word "aspirin" (Alberts, Tr. 8988; Miles, Tr. 9361).

1233. The most important factor in Bayer's image is its heritage, its longevity, the length of time it has been in the market. It is the original aspirin (Miles, Tr. 9361; Haley, Tr. 10651).

1234. Advertisers often refer to the original brand, the founding brand of the category, as having the "grandfather rights" because such brands have certain characteristics in common: greater longevity, long-term visibility; they stand for integrity, purity, reliability, honesty, trustworthiness and lack of risk. Such brands generally have overall favorable images among users and nonusers alike (Miles, Tr. 9362).

1235. These grandfather rights do not come from the content of advertising, although the visibility and continued advertising generally helps to maintain them (Miles, Tr. 9364, 9366).

1236. The grandfather rights provide to the brand image a high regard, an overall generalized favorability irrespective of use. This generalized feeling may be reinforced for both users and nonusers by advertising weight regardless of specific content, by visibility in stores and people's homes; sometimes by nostalgia (Miles, Tr. 9364, 9366).

1237. Complaint counsel's witness Dr. Ross acknowledged that Bayer is a product with a long-standing, reliable position or "franchise" in the consumer's mind, analagous to Gerber's Baby Food and others in their respective fields. Dr. Ross discussed this point with reference to products which have long-established market positions, illustrating with Gerber's Baby Food the fact that the mere mention

of a brand name may cause a consumer to bring an understanding of the product in mind. In this situation, "the advertiser need only mention the brand name and a substantial percentage of the audience may understand the message as 'Here we are again, old reliable Gerber's, the safest, most nutritious, most reliable baby food your baby can eat.' " (Ross, Tr. 5866–68, 5880–81).

1238. Dr. Ross also agreed that Bayer Aspirin had "lineage," described as familiarity with the product, "my mother **[303]** used it," the good old reliable standby used at home (Ross, Tr. 6059–62).

1239. The image of Bayer Aspirin is of a mild, middle-of-the-road, overall high quality, no risk product. It is regarded with a generalized, overall favorability, a good brand that has been around for a long time (Miles, Tr. 9364, 9373).

(a) *The Assets and Liabilities Study (CX 395)*

1240. The 1967 "Assets and Liabilities Study of Adult Analgesics" (CX 395) was designed by Dancer-Fitzgerald-Sample, Inc. (DFS), and executed by Crossley Surveys for Sterling Drug, Inc. Its stated purpose was to "provide assets and liability profiles for Bayer Aspirin and other leading brands of analgesics products" and to "serve as a 'benchmark' against which data for future assets and liabilities studies may be measured" (CX 395F; Miller, Tr. 209–10). It is a replication of an earlier study that Crossley Surveys had done for DFS (Leonard, Tr. 88–89).

1241. Lloyd Miller, who designed CX 395, was and is Vice-President and Associate Director for Research of DFS. Mr. Miller testified concerning the design and analysis of the study.

1242. The sample for this study was a "multi-stage stratified area sample." The sample design provides for the selection of individual respondents by dividing the country as a whole into smaller and smaller units, from major markets to minor civil divisions to blocks, and from blocks to households. "Stratification" refers to that control on the sample which insures that it accurately represented particular demographic attributes of the population as a whole. Such stratification related to sex (50% male and 50% female), and to geography. The sample was designed to be representative of the U.S. population in terms of the proportional representation of the four geographic regions, three sizes of standard metropolitan statistical areas and one size of nonmetropolitan counties in the U.S. (Leonard, Tr. 95–96). Thirty-five primary units, or markets, were selected from a national probability sampling frame of 80 primary sampling units to be representative of the whole United States. Within those 35 markets, Crossley Surveys selected minor civil divisions in proportion to their relative population (Leonard, Tr. 97–98). Within individual divisions,

urban block clusters were selected systematically from census block statistics whenever that was possible. Once a particular block was selected, a random technique was used to designate a starting point on the block for interviewers to commence their interviewing. From that starting point, interviewers were given explicit instructions on which houses to contact (CX 1007). These instructions left no discretion whatever in the hands of the interviewer (Leonard, Tr. 100). **[304]**

1243. The sampling procedure outline above is consistently used by Crossley Surveys. It yields results upon which marketing decisions are made (Leonard, Tr. 102–05). The procedure was discussed with, and explicitly approved by, DFS (Leonard, Tr. 102).

1244. The questionnaire for this study consisted of a notebook with 31 pages. Each page was a self-contained rating scale on a separate attribute, positive ratings at the top and negative ratings at the bottom. The rating of the products was to be made by the interviewees themselves inserting cards bearing the names of products into one of six pockets, corresponding to the intensity of their feeling about those products on each attribute (CX 395D, Z158–Z160).

1245. The design of CX 395 was similar to that of other image studies commissioned by DFS (Leonard, Tr. 86–88), and the "Assets and Liabilities" type of notebook-questionnaire used in this survey had been used by DFS since 1953 or 1954 for major clients such as General Mills and Falstaff Brewing Company (Miller, Tr. 214). This study design is comparable in quality to others for measuring images of products (Leonard, Tr. 94).

1246. CX 395 was executed according to Crossley Surveys' normal survey procedures. Most of the field work supervisors and interviewers on the project were people with whom Crossley Surveys had had substantial favorable experience (Leonard, Tr. 107). All interviewers were personally briefed by their supervisors and provided with detailed written instructions for administering the questionnaire (Leonard, Tr. 87, 107–10; CX 1000, 1002).

1247. Validation of interviews at Crossley Surveys was a two-step procedure, conducted both by interviewer supervisors and then by Crossley's headquarters (Leonard, Tr. 110, 115, 138–39; CX 1001). This process provided a total of 15% of total interviews validated. As a third check on the interviewers' work, DFS itself validated an additional 10% of the interviews (Miller, Tr. 229–30).

1248. Coding of the results of the survey was performed by Crossley's editing and coding department. A trained, experienced editor was normally responsible for that task. Given the absence of open-ended questions on the questionnaire necessitating interviewers' recording verbatim responses, coding for this project was a ministerial task. After the coding and editing tasks were accomplished by Cross-

ley, the results were delivered to DFS who analyzed them and prepared the report (Leonard, Tr. 115–16; Miller, Tr. 235).

1249. CX 395 was not conducted in anticipation of litigation. Sterling was DFS's client and requested the study **[305]** in the regular course of business. Sterling was satisfied with the quality of the work and its presentation (Miller, Tr. 209–10, 235–36). Crossley Surveys itself had no direct contact with Sterling nor any interest in any particular outcome of the study (Leonard, Tr. 87). As a result, there was no reason for the survey to be biased.

(b) *Study of Vanquish's Market Opportunities (CX 404)*

1250. The 1970 "Study of Vanquish's Market Opportunities" (CX 404) was designed by Benton and Bowles, Inc., an advertising agency for its client, Sterling, as part of the development of an advertising campaign for Vanquish. CX 404 was designed to measure consumers' attitudes toward analgesics in general, their opinion of some leading analgesic brands, including Vanquish, and to determine what sort of consumer Vanquish was most likely to attract (CX 404E). The backup data to CX 404 was received in evidence as CX 440.

1251. Joseph Pernica, the Associate Research Director and Vice-President of Benton and Bowles, Inc. at the time of the Vanquish Study had full responsibility for developing the design, methodology, and questionnaire for the survey, and for overseeing its execution (Pernica, Tr. 1893). He testified for complaint counsel concerning those substantive areas.

1252. Lieberman Research Corporation of New York was responsible for executing CX 404. Arnold Fishman, the Vice-President of Lieberman Research, testified for complaint counsel concerning the procedures used for conducting the study, including sampling procedures, interviewing, and coding and tabulating.

1253. The sampling procedure for the 1970 Vanquish Study, CX 404, was developed by Lieberman Research according to specifications set by Joseph Pernica of Benton and Bowles. These specifications included the sample size, the number and type of markets in which the survey would be conducted and the desired 50/50 sex distribution of the respondents. Benton and Bowles instructed Lieberman to investigate the Mid-Atlantic and Pacific region and also wanted to concentrate some interviews in three high-share Vanquish markets, Atlanta, New Orleans and Oklahoma City. Lieberman Research was given a list of cities in the Mid-Atlantic and Pacific regions to choose from and it chose the ones in which it had the best interviewers (Fishman, Tr. 1292–93; Pernica, Tr. 1918–19).

1254. Within each market chosen, the sample was randomly selected from addresses listed in telephone books. A random number was

picked as the one which to enter each phone book, and to get to successive pages, a skip interval equal to the number **[306]** of remaining pages divided by the number of desired interviewing clusters was determined. In order to minimize the sampling error due to use of telephone listings, interviewers were instructed to interview a resident of the house adjacent to the one picked from the phone book (Fishman, Tr. 1299–1301). This procedure left no discretion to the interviewer in selecting respondents.

1255. This sampling procedure was standard at Lieberman Research, and the sampling instructions given to interviewers were the company's standard written instructions (Fishman, Tr. 1339–40, 1300). It was not designed to produce a national probability sample. However, the degree of deviation from strict adherence to all probability standards in this sampling pattern was small enough that Lieberman typically recommended that marketing decisions could be made based upon the data generated (Fishman, Tr. 1367–68).

1256. The Vanquish Study (CX 404) was based on personal interviews. The questionnaire was carefully reviewed and revised by Arnold Fishman at Lieberman Research in order to eliminate ambiguities and to ensure correct question order. After it was put into final form, it was pretested in the field to ensure that it could be easily administered. The pretesting indicated that there were no significant problems with the interview (Fishman, Tr. 1295–97). Lieberman Research chose its interviewers and supervisors carefully, using only supervisors who were known to have done timely work of high quality in the past, and encouraging the supervisors to use only their best interviewers. The supervisors were responsible for training interviewers, for passing on Lieberman Research's standard written instructions, for acting as intermediaries between them and the central office, and for validation of the interviewer's work. Lieberman did not rely solely upon the supervisor's validation, but validated an additional fifteen percent (15%) of all questionnaires in the central office. If validation of an interview uncovered a problem, all of the work of the interviewer who conducted it would be validated. In addition to these two validations, a third validation check was run by an outside service to ensure objectivity (Fishman, Tr. 11317–18).

1257. Coding, keypunching and tabulations were performed by Lieberman Research according to its normal procedures for studies of this type. The codes for open-ended answers were developed by Lieberman Research's coding staff under Arnold Fishman's supervision. Joseph Pernica, of Benton and Bowles, approved the final codes (Pernica, Tr. 1929). A portion of every coder's work was checked by the coding staff supervisors to verify that coders were correctly interpreting verbatim responses (Fishman, Tr. 1319–21). Keypunching and

tabulations were performed by Data Probe, a research computer company selected by Lieberman Research with the approval of Benton and Bowles, Inc. All of the coded questionnaires were [307] "machine-cleaned" (checked for the logic of responses) and all the keypunching was verified as accurate by machine at Data Probe. Data Probe produced the tabulations of the results, CX 404, according to specifications set by Benton and Bowles, and Lieberman Research checked the tables for conformity with those specifications. Mr. Pernica received the tabulations from Lieberman Research and used them as the basis for his analysis presented in CX 404 (Fishman, Tr. 1321–25; Pernica, Tr. 1929–30).

(c) *1971 Advertising Penetration Study (CX 565)*

1258. CX 565 was designed and analyzed by Ted Bates & Company, Inc. ("Bates"), and was conducted by Valley Forge Information Service (hereinafter "Valley Forge"), a wholly owned subsidiary of Burlington Industries, at the request of and for the benefit of Bristol-Myers Corporation (CX 1019–1020). Its purpose was to measure the advertising penetration of Bufferin and other OTC analgesics (CX 565E-K, CX 1009). The questionnaire design is typical of earlier Bates penetration studies, many of which are also performed for Bristol-Myers Corporation. Employees of both Bates and Valley Forge testified that the questionnaire was typical of those used in assessing advertising penetration (Weitz, Tr. 731; Fratto, Tr. 810).

1259. Bates is the advertising agency for the Bristol-Myers Company for the Bufferin account. Ms. Anne Jack,[6] a Vice President of Bates, testified for complaint counsel regarding the design and analysis of CX 565. Bates' research department performs a wide range of research on all types of products for its clients (Weitz, Tr. 809).

1260. Valley Forge designed the sampling plan for this survey. The first step was the construction of a "master probability sample." This was obtained by dividing up the entire country, according to published photostats from the Census Bureau, first into a census region, and then into four city-size classifications within the census regions. The "sampling points" within the four city-size classifications are randomly selected from within the counties listed in each classification. While one could obtain any number of sampling points, the 100 points used in this survey were found more than adequate (Fratto, Tr. 737–38). [308]

1261. The telephone numbers of individual survey respondents were selected randomly from within these sampling companies for each county in the master sampling plan, a standing order being

[6] When Ms. Jack testified about CX 565, her name was Anne Weitz. Therefore all citations to her testimony refer to "Weitz."

placed with each company to ensure that the directories were recent. If, for example, 1,000 complete interviews were required, 2,500 numbers would be selected, 25 from each of the 100 sampling points in the master sample. A randomized "skip pattern" within each phone book, starting from a random starting point, would also be established (Fratto, Tr. 738–40).

1262. All interviewers were instructed orally about the correct way to select a particular column on a page and a particular number down in that column. In other words, the smallest detail was attended to as carefully as the drawing of the original master sample (Fratto, Tr. 739–41). In order to minimize a nonresponse bias, each number at which there was no response received two call backs (Fratto, Tr. 744).

1263. The questionnaire was quite easily administered, because it required no skips and only very simple probes (CX 1009). Nevertheless, all interviewers received both written and oral instructions in conducting the interviews (CX 1021; Fratto, Tr. 740).

1264. In addition, training of the interviewers involved actual testing of their ability by supervisors who had at least one year's experience in interviewing and who were experienced in dealing with people (Fratto, Tr. 724). This degree of care in conducting interviews was a standard procedure at Valley Forge (Fratto, Tr. 720).

1265. The interviewers' WATS lines were connected to a monitoring facility so that each interview could be listened to as it was conducted without the interviewers being aware of the monitoring process (Fratto, Tr. 742). In addition, all completed questionnaires were checked by Valley Forge's supervisors for thoroughness and accuracy. Finally, there would be a third check by a group of editors who would review the questionnaires before they were sent to the client (Fratto, Tr. 745).

1266. Coding, keypunching and tabulation were performed by Bates after it received the completed questionnaires (Fratto, Tr. 745). Because the questionnaires contained open-ended verbatim responses, Bates employees expended a large degree of time and effort in developing appropriate codes for the verbatims despite the fact that the basic framework for coding had been developed during earlier Bates market penetration studies (Weitz, Tr. 823–24; CX 1016).

1267. The mechanics of coding and tabulating were performed by hand by Ms. Jack herself and a trainee under her close supervision (Weitz, Tr. 826). **[309]**

(d) *The 1973 Headache Remedy/Pain Reliever Usage and Advertising Penetration Study (CX 553)*

1268. CX 553 was designed to determine current advertising penetration and usage levels of selected analgesics (CX 553C). The study

was designed, executed and analyzed by Sobel-Chaikin Research Associates at the request of and in cooperation with American Home Products Corporation (American Home) (Sobel, Tr. 461–64). Sobel-Chaikin Research Associates is the research division of Market Probe International (hereinafter, "M.P.I."), an organization formed in approximately 1974 to perform market research, computer analysis and data processing for manufacturers and advertising agencies (Sobel, Tr. 451–53).

1269. Charles Sobel testified for complaint counsel regarding both the design and the execution of CX 553 for which he had ultimate responsibility. Mr. Sobel is Senior Vice-President and Director of the research group at M.P.I., and the founder of Sobel-Chaikin Research Associates.

1270. The study design called for a telephone sample to be randomly selected from telephone books in 10 major urban markets (CX 553C, CX 1007; Sobel, Tr. 467–68). Interviewers in each market were assigned a random starting page in the telephone book for the market and were instructed to skip a random interval number in order to obtain each succeeding page (CX 1007). They were instructed to start at the top of the second column on each page and proceed down the column until they had completed a series of five interviews. These instructions clearly left no discretion to the interviewer in the selection of respondents (Sobel, Tr. 467–68).

1271. The questionnaire for this survey was short, and it was easy to administer because it contained few skip patterns for interviewers to follow (CX 553Z101–Z104). The questions were unambiguous and were directed both to advertising recall and usage of analgesics. The questionnaire was developed in consultation and with the approval of American Home, and it was typical of questionnaires used previously by Sobel-Chaikin for advertising penetration studies (Sobel, Tr. 461–62, 484).

1272. The survey was conducted according to standardized procedures followed by Sobel-Chaikin Associates in all their research work. All interviewers received extensive instructions regarding the administration of the questionnaire and were personally trained by supervisors who were known either to the principals of the firm or to one of their field supervisors, on the basis of prior favorable experience (Sobel, Tr. 471–72). **[310]**

1273. Completed interviews were validated in a two-step procedure. Supervisors were instructed to validate work received from all their interviewers. In addition, 15% of the completed interviews submitted by supervisors were validated by an outside validation service hired by Sobel-Chaikin (Sobel, Tr. 477–81).

1274. M.P.I.'s in-house coding department coded the responses on

the completed questionnaires. The task involved building codes for verbatim responses to open-ended questions on the questionnaire asking about advertising recall. The final codes were prepared by Mr. Sobel and were approved by American Home. Checks on the quality of coding were supplied by M.P.I.'s coding supervisor and by having individual coders re-do each other's work for comparison purposes (Sobel, Tr. 483–85; CX 1005, 1006).

1275. M.P.I.'s own data processing group keypunched the completed questionnaires. The keypunching was performed by experienced operators and was checked both by verification and by automatic controls placed into the computer programing that produced the tabulation runs. The tabulation plan was developed in accordance with specifications approved by American Home. The report of CX 553 was prepared by Mr. Sobel and as submitted to American Home (Sobel, Tr. 484–87).

(e) *Zeisel Image Study (CX 521)*

1276. The purpose of CX 521, "The Consumer's View of the Relative Effectiveness of Various Brands of Aspirin" (Zeisel Image Study) was to identify consumers' images of the relative effectiveness of various brands of 5-grain aspirin. More specifically, CX 521 measures the comparative image of Bayer compared to other brands of aspirin with respect to effectiveness and speed of relief (Zeisel, Tr. 4649; Crespi, Tr. 4341; CX 521B). This study was conducted for use in this litigation by Dr. Hans Zeisel and the Gallup Organization under contract with the FTC.

1277. The principal author of CX 521 is Dr. Hans Zeisel. Dr. Zeisel was primarily responsible for the design of the study, the design of the questionnaire, the designation of samples, and the drafting of the final report (Zeisel, Tr. 4650–01). The Gallup Organization and Dr. Irving Crespi, then of Gallup, participated in the design questionnaire and executed the fieldwork for the study (Crespi, Tr. 4341; Zeisel, Tr. 4722–23). The fieldwork for CX 521 was conducted in substantially the same fashion as the fieldwork for CX 520, the Zeisel Copy Tests (Crespi, Tr. 4345–52).

1278. Dr. Crespi reviewed the draft questionnaire to CX 521 and pretested it to see that it conformed to good professional practice. The pretest indicated that, without exception, the [311] questionnaire was professionally acceptable. The pretest did show that some respondents failed to rate a brand of aspirin because they had never used that brand. Because the objective of the study was to measure images of brands among consumers who were familiar with a particular brand regardless of whether or not they used it. Question 4 was revised, explicitly instructing respondent to rate all the brands he or she was

familiar with regardless of whether or not the respondent had used the brand. With this change, the final questionnaire in CX 521 (CX 521Z002–Z005) fully conformed to good professional practice and was considered to be a "state of the art" questionnaire for consumer image research (Crespi, Tr. 4341–45).

1279. All surveys based upon probability samples are subject to sample error. "Sample error" is the measure of the extent to which the survey results may differ from the "true value" that would be obtained if the whole population was interviewed. Appendix III of CX 521 sets forth the estimated "sample error" at the 95% confidence level for the percentages reported in CX 521. Appendix III indicates the range (plus or minus the figure shown) within which the results of repeated sampling will occur 95 times out of 100 (CX 521Z014; Crespi, Tr. 4324–25, 4347).

1280. The response rate to CX 521 was about 60%. This response rate meets generally accepted standards for research of this nature (Crespi, Tr. 4351).

1281. The interviewers' work was validated by Gallup in the same manner as set forth in F. 219 (Crespi, Tr. 4350). The final and completed questionnaires were put through a standard quality control procedure to verify that the interviews had been conducted in accordance with instructions. The answers to CX 521 were statistically weighted according to demographic characteristics. This procedure is described in F. 221, *supra* (Crespi, Tr. 4351–52).

1282. The tabulated results of responses to the questions asked in CX 521 are set forth in Tables One through Nine (CX 521I-Y).

1283. After the Gallup interviewer selected the designated person within the household to be interviewed, the respondent was first asked whether he or she uses pain relievers. If the answer was "no," then the interview was terminated (Crespi, Tr. 4346). For those who indicated that they used pain relievers, they were then asked what brands of aspirins they have ever heard of or bought. The Gallup interviewer recorded all such responses. Next, the respondent was given a set of cards, each of which contained the name of a brand of aspirin, and then was asked if he or she had ever bought or heard of any of those brands of aspirin. The brands on the cards were A&P, Bayer, McKesson, Norwich, Rexall, Safeway, Squibb, St. Joseph's Aspirin [312] for Adults, and Upjohn. The Gallup interviewer then recorded all such responses. If the respondent mentioned two or more brands of aspirin, the respondent was then asked to rate on a scale of one to ten how effectively and how quickly those brands work. Finally, standard brand usage and demographic questions were asked of the respondents (CX 521G, Z002–Z005; Zeisel, Tr. 4726–33).

1284. There were 501 respondents interviewed in CX 521 (CX 521G).

Respondents were selected on a random, probability basis for Gallup's master probability sample as set forth in F. 217, *supra* (Crespi, Tr. 4345; CX 521Z009–Z012).

1285. The purpose of CX 521 was to determine how consumers of pain relievers viewed the various brands of aspirin which they had bought or heard of (CX 521B). The brand image of Bayer vis-a-vis various other plain 5–grain aspirin products were studied. A brand image is a group of general impressions that people hold about a particular brand. It is the personality or character of a brand (Miles, Tr. 9355; Haley, Tr. 10567, 10605–10; Lipstein, Tr 12228).

1286. Respondents argue that there are literally dozens of factors that are involved in brand imagery: favorable or unfavorable experience with the brand word-of-mouth; nonverbal communication, such as the package, graphics, name, or price; favorable or unfavorable publicity; sheer longevity and visibility in the market; the amount of advertising regardless of content; advertising content; product innovation; store displays; promotional activities, and other sources. A brand image is not a direct reflection of advertising (Miles, Tr. 9355–59; Haley, Tr. 10567, 10605–10; Lipstein, Tr. 12037).

1287. However, the crucial determination is not whether there is a multitude of sources for a particular brand image, but rather, whether advertising "in part" created a false impression or "played a substantial role in creating or reinforcing" a false and material belief. *Warner-Lambert Co.*, 86 F.T.C. 1398, 1499, 1503 (1975).

1288. The role of advertising in the formation of brand images varies according to the age of the brand. Newer products have images that are more malleable (Haley, Tr. 10569, 10651).

1289. The results of CX 521 are projectable with acceptable confidence to the total noninstitutionalized U.S. population of persons 18 years or older who use over-the-counter pain relievers (CPF 148–159; Crespi Tr. 4345).

1290. Subjects were asked to identify all brands of plain 5–grain aspirin products they had ever bought or heard of. To the extent that subjects did not recall on an unaided basis any of **[313]** nine nationally available aspirin brands, they were asked if they had ever bought or heard of those brands on an aided basis by being shown cards on which were printed the brand names (CPF 152; Zeisel, Tr. 4726–29). Subjects were then asked in questions 4 and 5 of the survey to rate each of the brands they recalled, whether they had used the brand or not, first on the basis of "how effectively it relieves pain," and second "how quickly it relieves pain," on a ten-point scale with a verbal anchor at the tope, "outstanding" (10), and at the bottom, "very poor" (1) (CPF 152; Zeisel, Tr. 4731–33). The use of ten points and verbal anchors were appropriate in the context of this survey (Crespi, Tr. 4342–44).

Data from these two questions were generated by considering simply whether each subject rated each brand higher, lower, or the same on each scale vis-a-vis Bayer, regardless of what points (s)he chose on the scales for the brands rated. Data for this question is reported as percent of ratings of Bayer as higher, the same, or lower than other brands (Zeisel, Tr. 4742–43; CX 521M, Q). The percent of consumers who hold comparative images of two products can be assessed by determining their beliefs about *both* products (CX 521; Ross, Tr. 5828–29). The sixth question asked which brands of pain reliever each subject used "most often." If the subject failed to identify a plain 5–grain aspirin product, (s)he was asked if (s)he ever takes aspirin and if so, what aspirin. With respect to the percentage of respondents who indicated that they used Bayer most often, the study separately reported their images on effectiveness and speed of relief (Zeisel, Tr. 4738–39; CX 521V, X).

1291. As an initial step in the analysis of the data generated in CX 521, the Zeisel Copy Tests, responses were assigned sample weights. This is done routinely by large survey organizations in national probability samples to adjust for discrepancies between the population in fact sampled and what the actual U.S. population is like. These estimates of what the U.S. population is like are based on annual census reports on population demographics such as age, sex, education or region of the country. Weights are assigned to responses in order to bring the characteristics of the survey population as close as possible to the U.S. population (Crespi, Tr. 4339–40, 4352). By inadvertance a few respondents were assigned "0" weights, which effectively eliminated their responses from the study. This error was insignificant and affected none of the results by any more than 1% (Crespi, Tr. 4362–63; Zeisel, Tr. 4819–20).

1292. Several criticisms of the Zeisel image study, CX 521, were offered by respondent's witnesses. The first criticism was that Dr. Zeisel had failed to take into account the possible relationship between the subject's brand awareness **[314]** and his rating (Amstutz, Tr. 10095). A second, related criticism was that CX 521 made no adjustment for the "halo" phenomenon (Haley, Tr. 10599). A third criticism was that the ten-point rating scale was inappropriately long (Haley, Tr. 10600). A fourth was that the results of CX 521 are explainable by the phenomenon of user loyalty.

1293. Dr. Amstutz was the major proponent of the argument that the Zeisel image study failed to consider brand awareness vis-a-vis rating. He undertook to remedy this in RX 142, a reanalysis of data from CX 521 prepared under his supervision (Amstutz, Tr. 10096). Dr. Amstutz's approach was to analyze ratings depending on whether subjects' recollection of brands was unaided, probed or aided, and

depending on whether subjects placed the brands they rated on the 1–5 end of the scales as opposed to the 6–10 end. His assumption in making the latter cut in the data was that a 1–5 rating is a low rating for any aspirin and a 6–10 rating is a high rating (Amstutz, Tr. 10397–99).

1294. This assumption was rejected by another of respondent's witnesses, Professor Russel Haley, who characterized as inaccurate a procedure whereby all the 6–10 ratings are treated as high and all 1–5 ratings are treated as low (Haley, Tr. 10704). People use scales differently; one person's "5" could be a high rating to him or her whereas another person's "6" could be low. CX 521 accounts for these differences between subjects by considering each person's relative ratings separately, each subject in effect becoming his own control (Haley, Tr. 10696).

1295. Thus the process used by Dr. Zeisel reduces concern for error in analysis that arises from the fact that different people use different portions of the scale or don't use all points of the scale (Haley, Tr. 10704). In any event, regardless of any error in the reanalysis done in RX 142 caused by Dr. Amstutz's division of the data into 1–5 and 6–10 ratings, Dr. Amstutz conceded that the relationship of subjects ratings of brands and their brand familiarity in RX 142 does not exclude the possibility that there are other factors than awareness, such as advertising content, that are leading to the efficacy ratings (Amstutz, Tr. 10435).

1296. Dr. Haley testified that the ten-point scale used in CX 521 is one shown by research to be less reliable because it uses too many points. Respondents were given too many choices and experience shows that it is dangerous to give any significance to a one-point difference on this type of scale (Amstutz, Tr. 10118; Haley, Tr. 10600–01; CX 521Z006, Z007).

1297. Professor Haley's testimony with respect to his concern about the length of the rating scales used in CX 521 seems to conflict with his previously expressed views. Despite [315] the fact that he testified that the ten-point scale with verbal anchors used by Dr. Zeisel was "not usual," Professor Haley admitted that in his article, CX 709 for identification, "Testing Thirteen Attitude Scales for Agreement and Brand Discrimination," published in the Fall 1979 Journal of Marketing, he evaluated a ten-point scale with verbal anchors as "commonly used" (Haley, Tr. 10693). He also conceded that when a numerical scale is used subjects have to be given verbal instructions so that they know which end of the scale is good and which end is bad because otherwise some subjects might regard ten as highest and others regard one as highest (Haley, Tr. 10695). Moreover, Professor Haley's opinion concerning the ten-point scale was contradicted by other ex-

pert testimony. Dr. Irving Crespi, an expert in the design and execution of consumer research and an expert with considerable experience with the use of rating scales such as those used in CX 521, said that the scales here were appropriate under the circumstances (Crespi, Tr. 4311, 4342–44). Dr. Amstutz acknowledged a variation of opinion regarding ten-point vs. six-point rating scales (Amstutz, Tr. 10286).

1298. Respondent also argues that there are other significant problems with the rating scale itself: For example,

(a) The scale used in CX 521 is also less reliable because it combines both words and numbers. In this situation, some people will use the words; others would use the numbers; while still others would use a combination of the two. Put together, they are not additive in statistical terms, and if the scale were repeated the next day with the same person, he might change from words to numbers or vice versa, and give different reactions. It is much better to utilize either numbers or words (Haley, Tr. 10600–01; *see* CX 521Z006, Z007).

(b) When shown the scale, consumers will think they are rating overall quality, not effectiveness or speed (Haley, Tr. 10715; *see* CX 521Z006, Z007).

(c) A substantial problem with the scale is the verbal anchors themselves. On the effectiveness scale, CX 521Z006, the verbal anchors should have been a phrase related to effectiveness, such as "completely effective" and "completely ineffective," rather than the overall general terms, "outstanding" and "very poor," that were used. Similarly, on the speed scale, CX 521Z007, the verbal anchors should have been something like "extremely fast," "extremely slow," rather than the same overall general terms, **[316]** "outstanding" and "very poor" (Miles, Tr. 9676; Haley, Tr. 10601; Lipstein, Tr. 12207–08; *see* CX 521Z006, Z007).

(d) Based on Dr. Haley's experience in scaling, when a scale says "outstanding" to "poor," people tend to give an overall evaluation. This is borne out by the similarity of the results obtained in the two questions (Haley, Tr. 10676; RPF 6.111; *see* CX 521N, P).

(e) Respondents would have focused on the scale itself and were unlikely to notice the heading at the top of the page. The respondents would not look to the top because their attention would be focused on the scale to try and understand the task they were asked to perform, particularly if it was unfamiliar to them (Haley, Tr. 10716; *see* CX 521Z006, Z007).

(f) The format of the two scales is so similar that it is likely that people will not note the change in the one word in the heading from "how effectively does it relieve pain" to "how quickly does it relieve pain." The data bears this out. The results of the two scales questions

are almost identical (Haley, Tr. 10601, 10676; *see also* Lipstein, Tr. 12207–08; Miles, Tr. 9416; CX 521N, P).

(g) In addition, the method of administration compounds the problems caused by the use of the scale. The interviewer reads a long paragraph to each respondent which, although briefly mentioning "effectiveness" and "speed" at the beginning, explicitly referred to the verbal anchors "outstanding" and "poor" throughout the instructions, concluding with the statement: "Rate them just the way you feel about each brand." This will lead to an overall rating by the respondent in terms of whether the brand is considered to be "outstanding" or "poor," rather than ratings related to "effectiveness" and "speed" (Haley, Tr. 10602–03; Lipstein, Tr. 12207–08; *see* CX 521Z004).

(h) If meaningful verbal anchors such as "relieves pain effectively" and "does not relieve pain effectively" had been used, they would have tied respondents to the scale and focused them on the issue of concern, instead of inviting them to rate a brand according to a general reputation or [317] aura, *e.g.,* a high rating for a national brand (Amstutz, Tr. 10118–20).

1299. However, the evidence is persuasive that the design of CX 521 is basically sound for the purpose for which complaint counsel seek to rely on in this proceeding, although care must be taken in interpreting the responses to the various questions.

1300. Respondent's expert witness, Dr. Amstutz, testified that, in his experience, users of a product are more apt to give their brands higher positive ratings on generic attributes (Amstutz, Tr. 10125–26; RX 142M, Table H).

1301. CX 521 is useful in judging consumer images of Bayer's relative effectiveness and speed vis-a-vis other plain 5-grain aspirin in 1975. Results of CX 521, reported at page C, as corrected by Dr. Zeisel on November 13, 1979) were that 40% of consumers (weighted) rated Bayer higher than all other brands with regard to effectiveness; 39% rated Bayer higher with regard to speed of relief. Of the remainder 34% and 35% respectively rated all brands equally on effectiveness and speed and 15% and 13% respectively rated Bayer highest with other brands. These results are projectable to the noninstitutionalized U.S. adult population who use OTC pain relievers.

1302. In his evaluation of the Bayer image in 1975, Dr. Ross considered responses to questions 4, 5 and 6 of CX 521 (Ross, Tr. 5826). Dr. Ross prepared a chart, CX 541, in order to look at the image of Bayer compared to other aspirin in a way that removed or adjusted for user bias. This chart incorporates an analysis of the way in which Bayer was rated among its users and the way other aspirin brands were rated by their respective users (Ross, Tr. 5827).

1303. In order for a respondent to be included in CX 541 (s)he would have had to have rated another brand besides the one (s)he used most often now. In other words, the respondent must have had a belief about more than one brand in order to qualify as having a comparative image (Ross, Tr. 5828–29). Results reported at page CX 541A demonstrate that 80 out of 136 respondents who reported that they now used Bayer most often rated best in effectiveness, while only 3 of 35 who now used another brand most often rated that brand above all others on that attribute. Eighty out of 136 versus 3 out of 35 is "clearly" statistically significant, though Dr. Ross went on to confirm this by performing a chi square analysis (Ross, Tr. 5828–29). This analysis showed that the image of Bayer among its users is superior in terms of efficacy compared with the image of other 5–grain plain aspirin among its users (Ross, Tr. 5829; CX 541A).

1304. Dr. Ross performed the same analysis on the attribute "speed," reported at CX 541B. Here, 74 out of 135 rated their [318] product, Bayer, as best compared with other aspirin as opposed to the 5 out of 35 who rated their non-Bayer 5–grain aspirin as best. The lopsided nature of the difference in the "speed" image of Bayer among its users, compared with other aspirins' speed images among their users, led to a statistically significant chi square value (Ross, Tr. 5829; CX 541A-B). Both speed and effectiveness results led Dr. Ross to conclude that the image of Bayer is superior to the image of aspirin on these measurements of effectiveness (Ross, Tr. 5829).

1305. CX 541 was prepared to account for user bias (Ross, Tr. 5827, 5829). According to Dr. Ross, these tables remove whatever contribution user bias might have had to the ratings by consumers because the analysis looks only at the image of each brand among its respective users (Ross, Tr. 5829). From CX 541, Dr. Ross concluded that, in 1975, the image of Bayer versus other plain 5–grain aspirin, was that Bayer was a superior product with respect to effectiveness and speed (Ross, Tr. 5830). Because speed is an indicium of effectiveness, Bayer was viewed generally as superior in terms of effectiveness (Ross, Tr. 5830).

1306. Dr. Ross testified that his conclusion that consumer images of Bayer's superior therapeutic effectiveness are not a consequence of user bias is supported by Tables 8 and 9 of CX 521 appeared at pages X and Y. Table 8 shows that 24% of the respondents not using Bayer rated it "best" as against other aspirin in terms of effectiveness; 23% of respondents not using Bayer rated it best in terms of speed. These nonusers could not have had their images of Bayer contributed to by usage of the product. Therefore, the image must have come from some other source, not use (Ross, Tr. 5830–32; CX 521X and Y). This data led Dr. Ross to conclude that a substantial number of people held an image of Bayer in 1975 that it was therapeutically superior to other

aspirin and this image would not be explained as a result of use or user bias (Ross, Tr. 5832).

1307. Two advertising penetration studies in evidence, the 1971 Ted Bates Advertising Penetration Study (CX 565), and the 1973 Sobel-Chaikin Study (CX 553), included questions related to Bayer Aspirin advertising penetration. Both surveys asked subjects to identify what recent advertising said about Bayer Aspirin. The 1973 study (CX 553) differed slightly from CX 565 in that it asked first whether the subject had seen or heard any recent advertisement for any headache remedies or pain relievers, and if so, what. This question generated an "unaided" response, *i.e.,* a response that was elicited by a question that made no reference to any product. Respondents were then asked whether they had seen any advertisement for specific products by brand name, including Bayer. Neither "aided" question in either study (*i.e.,* aided in the sense that the questions referred to brand names such as "Bayer") added anything to suggest the content of the advertising (Ross, Tr. 5810–11). **[319]**

1308. Evidence from CX 565 (the Ted Bates Advertising Penetration Study) confirms that consumers remembered Bayer's competitive effectiveness claims. Page K of CX 565 shows that 48% of the sample surveyed reported recall of Bayer advertising, and 16% of the sample recalled claims of competitive superiority for Bayer ("Competitive Superiority, Net"). It is not known exactly what was tabulated within that 16%. However, Page U, showing breakdowns of "Net Competitive Superiority, 16%," indicates that the therapeutic superiority category with respect to Bayer could be as low as 3% ("stronger" and "safer") or as high as 5% ("stronger", "safer" and "more relief"). The 8% shown for "Better/best/more effective" on S may also indicate the upper limit of "therapeutic superiority" recall, although the probability that 8% may include "better/best" in "better/best for quality," sense as some pre-1970 Bayer advertisements expressly claimed, cannot be excluded.

1309. With respect to CX 553, the 1973 study, about 51% of the respondent recalled Bayer advertising (Ross, Tr. 5811). Other tabulations show that therapeutic superiority claim recall for Bayer could be as low as 8.6% ("faster acting" - CX 553Z46) or as high as 25.1% ("best, better than other aspirin" - CX 553Z46), although there is a distinct likelihood that the 25.1% figure would also include "best, better than other aspirin for quality" as most of the Bayer advertisements in the early '70's expressly claimed. However, Dr. Ross found no penetration of advertising themes relating to manufacturing quality in CX 553.

1310. Thus, the advertising penetration data in evidence generally

show that a significant portion of consumers in the 1970's remembered Bayer's claim of therapeutic superiority.

1311. In the context of analgesic advertising, when consumers believe that the attributes of a particular OTC product make it perform better (*e.g.*, faster, safer, or more effectively than another product), they also believe that the superiority of that product on those attributes has been supported by scientific evidence (Ross, Tr. 5756). Were this not the case, consumers assume that the advertiser would be prohibited from making that statement, most typically, by the government (Ross, Tr. 5756). Dr. Ross' opinion in this regard is confirmed by a Food and Drug Administration study entitled "A Study of Health Practices and Opinions" dated June 1972. At page 270 the survey reported that 38% of American adults agreed with the statement, "Most of the things that advertisements say about medicines and health aids must be true or they wouldn't be allowed to say them" (Ross, Tr. 5766).

1312. Consumers hold beliefs about products and services (Ross, Tr. 5815). Those beliefs are measured in terms of [**320**] attributes or dimensions or characteristics of the product. Consumer attitudes are measured in terms of both the nature of the content of their beliefs and the effect or desirability of their beliefs (Ross, Tr. 5815). The most typical way of measuring consumer images or beliefs is to conduct a consumer survey, an image study, to measure the nature of those beliefs through either open-ended or close-ended responses (Ross, Tr. 5816; Crespi, Tr. 4341).

1313. Dr. Ross selected from CX 395 18 attributes from among the 33 that were asked about, attributes that he felt were most pertinent to evaluating consumer beliefs about relative therapeutic benefits of aspirin products (Ross, Tr. 5817). CX 637, "Usage and Selected Image Characteristics of Bayer, Norwich and Store Aspirin," is a table of attributes from CX 395 that Dr. Ross considered (Ross, Tr. 5819). Dr. Ross considered attributes such as "never upsets your stomach," "relieves pain most quickly," "relieves pain for a long time" as pertinent to consumer beliefs concerning therapeutic superiority (CX 637), and attributes such as "hear about it all the time," "high priced brand," or "a company that cares about the consumer," as not pertinent. This was an appropriate selection of data for purposes of the complaint. CX 521 was already composed of a question specifically dealing with effectiveness and a second one dealing with speed which Dr. Ross felt were appropriate attributes to look at for purposes of the complaint (Ross, Tr. 5816–17).

1314. Dr. Ross prepared CX 637 for the purpose of removing biases that are inherent in studies such as CX 395. This bias must be accounted for in order to arrive at a conclusion about the comparative

image of brands in a survey in which there are different numbers of brand users of the brands in the survey. Dr. Ross regarded user bias to be unfair where, as in CX 395, there were more exclusive users of Bayer than there were users of other brands in the survey. Without adjusting for the fact that there are different brand shares, an analysis of CX 395 would "load the dice," as it were, for many attributes for the brand that was most popular (Ross, Tr. 5820). Since Dr. Ross lacked the underlying data to perform what he regarded as the preferred adjustments—either to calculate the user image of Bayer and contrast it with the user image of Norwich or store, or to calculate the respective brand image of Bayer, Norwich and store among nonusers of each respective brand—what he did was to first determine the number of exclusive users of each brand and subtract those percentages from the percentages who rated particular attributes of the respective brands as "top pocket" (Ross, Tr. 5820–21). The term "top pocket" refers to the method of eliciting data. Subjects in CX 395 were asked in each **[321]** question to express their preferences by placing cards with brand names printed thereon in one of six envelopes or "pockets" ranged vertically on a page, at the top of which was printed a verbal anchor such as "relieves pain for a long period," and at the bottom of which was printed "relieves pain for a short time" (CX 395D, Z158–Z160).

1315. In performing these calculations Dr. Ross realized that some results would be illogical (Ross, Tr. 5821). For example, only 29% of Bayer users regarded Bayer as top pocket for the attribute "relieves pain for a long period." If one subtracts the 36% exclusive Bayer users figure from the 29% top pocket figure, the result is −7%, which is inexplicable from the viewpoint of a real number in this context (Ross, Tr. 5821). Nevertheless, despite the inadequacies of this adjustment in some cases, it was the best procedure available to Dr. Ross to remove user bias given the absence of underlying data (Ross, Tr. 5820–21). Dr. Ross followed a similar procedure for the other brands, subtracting the 2% exclusive Norwich users from the Norwich top pocket data, and subtracting 7% exclusive store brand use from the store brand top pocket data (Ross, Tr. 5823).

1316. As a last step, Dr. Ross calculated the statistical significance of differences in the adjusted top pocket ratings between Bayer, Norwich and store for all but two of the 18 attributes listed on CX 637 (two attributes, "good for relieving nervous tension" and "good for premenstrual/tens/depression," he decided were not relevant to therapeutic superiority allegations of the complaint (CX 637; Ross, Tr. 5822). He used a common statistical test known as a chi square, at a 90% confidence interval (10% alpha level). The results were reported

at CX 637 in the far right column headed "differences" (Ross, Tr. 5823).

1317. Dr. Ross found that for five of the characteristics Bayer was superior in image to both Norwich and store brand as follows: often recommended by doctors, never upsets the stomach, good for occasional mild headaches, effective in reducing fever, and good for aches and pains of colds and flu (Ross, Tr. 5824). Bayer's image was superior to store but equal to Norwich on two attributes: relieves pain most quickly and good for all kinds of pain (Ross, Tr. 5824). Bayer was inferior to either Norwich or store or both on several attributes: strength or strong product, and specialized kinds of pain such as muscular and arthritic pain (Ross, Tr. 5825).

1318. Based on his analysis of top pocket attributes on which Bayer was superior and those where it was not, Dr. Ross concluded from CX 395 that Bayer was believed by consumers to be a superior general pain reliever, but it was not seen as comparatively strong aspirin nor as a unique, distinctive or specialized pain reliever compared to other aspirin (Ross, Tr. **[322]** 5825). Dr. Ross viewed the fact that Bayer was rated higher on the "often recommended by doctors" measure than competing aspirins as relevant to the establishment component of the case (Ross, Tr. 5825).

1319. Two image studies in evidence, CX 395, the 1967 "Assets and Liabilities" Study, and CX 521, the Zeisel Image Study (conducted in 1975 and reported in 1976), were relied on by Dr. Ross in reaching an opinion about consumer beliefs about the therapeutic superiority of Bayer Aspirin to other plain 5-grain aspirin. Dr. Ross concluded from his analysis of CX 395 and 521 that a significant number of consumers believed that Bayer is therapeutically superior to other aspirin (Ross, Tr. 5816). This conclusion is reasonable and is supported by a preponderance of credible evidence in the record.

B. *The Record Evidence Is Insufficient To Show That Respondent's Unlawful Advertising Claims Played a Significant Role in Creating and Reinforcing Consumers' Beliefs in the Therapeutic Superiority of Bayer Aspirin Over Other Plain Aspirin During the Relevant Period*

1320. A variety of factors contribute to the creation or reinforcement of an image about a product. The most frequently mentioned factors in the professional and trade literature are usage, advertising, word-of-mouth, the package, news stories in the media, and the store in which it is bought (Ross, Tr. 5832). Of these, the literature in the field of marketing regards usage and advertising as the most likely source of product image (Ross, Tr. 5832–33). Word-of-mouth generally

derives from usage or advertising, so that it is not regarded as a separate source of image (Ross, Tr. 5833).

1321. Advertising creates expectations for consumers about what benefits are to be achieved or realized through the use of the advertised product (Ross, Tr. 5833). If the consumer buys the product, advertising will guide or assist the consumer in coming to some impression or conclusion about what the product is like. It will guide their perceptions as to how the product is performing (Ross, Tr. 5833). Advertising creates expectations about product performance which then translate into either causing people to try the product, or, if they are already users of the product, reinforcing images or beliefs that consumers already have about the product (Ross, Tr. 5833).

1322. If a product permits the consumers to evaluate it correctly, in the sense of sensory or physical qualities of the product, that will be the primary basis of consumer image or attitudes towards the product (Ross, Tr. 5834). Most consumers will trust their own senses as a basis of evaluating a product more than they will advertising or someone else's word for it. For most products and services, direct user experience or **[323]** perception of that experience is the basis of the image for that product (Ross, Tr. 5834).

1323. It is more difficult for consumers to evaluate the comparative performance of a product than it is to evaluate the absolute performance of a product (Ross, Tr. 5836–37). This difficulty is compounded where, as here, the product is a pain reliever and the consumer's only bases for evaluation are his own possibly uncertain recollection of past pain experiences, which may vary from time to time (Brock, Tr. 5163–65), and the effects of different analgesics, which may be indeterminate because of the subjective nature of individual response to pain and analgesia and the placebo effect.

1324. When a consumer cannot evaluate the performance of a product by virtue of his or her own sensory abilities, especially in a comparative sense, then direct usage experience will play an increasingly lesser role as sensorially discernible differences among brands in a product category became more indistinct (Ross, Tr. 5837). When the differences in performance between products in the brand category tend to be small, then the role of advertising in forming comparative images about the products tends to increase. In other words, as usage diminishes in its ability to be a contributor to the image of a product, then so does advertising increase in its role as a contributor to that image (Ross, Tr. 3838). The inability of consumers to evaluate the performance of drugs or, as here, the comparative performance of drugs, is supported by classical psychological research which shows that user "perceptions" of the drugs are influenced not by actual

product performance but by external information, such as advertising (Brock, Tr. 5054).

1325. In circumstances such as use of OTC analgesics, where usage cannot be appropriately evaluated by consumers, usage experience cannot explain away images that consumers hold about the product. Their expectations are, by definition, confirmed or supported when they use the product (Ross, Tr. 5838). Since usage and advertising are the most important sources of product image, the unimportance in fact of usage and comparative usage experience to the consumer in his or her formation of images of over-the-counter internal analgesic brands leaves the advertising induced expectations of performance as the major source for the creation and reinforcement of consumer beliefs about OTC analgesics.

1326. Dr. Ross, complaint counsel's witness, concluded that Bayer advertising disseminated between 1969 and 1974 served to either cause or to reinforce or contribute to Bayer's superior therapeutic image (Ross, Tr. 5841). The basis for this conclusion included his view that virtually all Bayer advertisements disseminated during this period represented that Bayer was therapeutically superior to other aspirin. This view is contrary to F. 293–294, *supra;* F. 1335, *infra.* Dr. Ross [324] also relied on the penetration studies (CX 553, 565) regarding what consumer recollections were present, and the "Assets & Liabilities" (CX 396) and "Zeisel image studies" (CX 521) which showed that the image of Bayer is that it is therapeutically superior to other aspirin (Ross, Tr. 5841). Moreover, in Dr. Ross' view, the image studies in evidence show that both users and nonusers hold essentially the same belief about the superior therapeutic performance attributes of Bayer.

1327. The evaluation of Dr. Ross' testimony as a whole makes clear that his conclusion that advertisements played a substantial role in creating or reinforcing the therapeutic superiority image of Bayer rests mainly upon his view that therapeutic superiority of Bayer was the dominant theme of all Bayer advertisements disseminated between 1969 and 1974. The administrative law judge, however, found that a relatively small number of the advertisements in evidence covering that period can be said to contain a therapeutic superiority claim.

1328. To the extent CX 521 (the Zeisel Image Study), conducted in 1975 and reported in 1976, noted a higher level of therapeutic superiority image for Bayer than the image data found in CX 395, reported in 1967 (and before the bulk of the advertisements in evidence were disseminated), it is arguable that the post-1967 Bayer advertisements played a significant role in raising the level of Bayer's therapeutic superiority image.

1329. The record shows, however, that CX 395 (the 1967 Study) is likely to have significantly understated Bayer's therapeutic image vis-a-vis other plain 5–grain aspirin brands (which is in issue in this proceeding). CX 395 essentially presented rankings by consumers of the then five major national OTC analgesic brands (Bayer, Alka Seltzer, Anacin, Bufferin and Excedrin) as well as Norwich aspirin and a catchall category called "Store's Own Brand." Although data for Norwich and Store's Own Brand were included for some thirty-three attributes, the in-depth analysis based on user/nonuser breakdowns was presented only for four major nationally advertized brands, Bayer, Anacin, Bufferin and Excedrin (CX 395, Z146–Z153). Thus, the study had as its thrust the image of Bayer as compared to the combination products, and the inclusion of only two possible aspirin brands undoubtedly shifted the focus of Bayer's comparative therapeutic image rankings away from aspirin brands. It is fair to say that CX 395 collected the Bayer-Norwich-Store's Own Brand data only incidentally, and as a result substantially understated Bayer's relative position vis-a-vis other plain 5–grain aspirins. In this light, the rise in Bayer's comparative image from 1967 to 1975 shown in CX 521 appears less significant.

1330. In this connection, what is noteworthy of CX 521 is that the proportion who rated all aspirin brands alike or other **[325]** aspirins better than Bayer in terms of effectiveness and speed of relief, were significantly greater than those who rated Bayer better. *See* CX 521C, Table.

1331. More importantly, the analyses of CX 521 data by complaint counsel's expert witnesses made no distinction whatsoever between Bayer, which is the only nationally advertised and distributed brand of plain 5–grain aspirin, and eight other aspirin brands, all regionally distributed brands and none of which does any advertising to speak of. Thus, complaint counsel's experts totally ignored the well recognized fact that consumers generally consider national brands or advertised brands to be superior products over local brands or unadvertised brands (Miles, Tr. 9397–98, 9598–99; Haley, Tr. 10577; Lipstein, Tr. 12028–29). It is especially difficult to compare Bayer to any of the other regional or unadvertised brands, and the user/nonuser analysis performed by Dr. Ross does not remove this difficulty.

1332. It is common knowledge that Bayer aspirin was introduced in this country during the early 1900's and has been the only plain 5–grain aspirin tablets marketed for some time. In fact, "aspirin" was a trademark identified with Bayer Aspirin for a long time. Since other aspirin brands were introduced, Bayer aspirin has remained the only nationally advertised and nationally distributed plain 5–grain aspirin. In these circumstances, one would expect consumers to be very

familiar with Bayer Aspirin independent of personal usage of the product or of personal exposure to any of the Bayer advertisements found to contain a therapeutic claim. It is fair to conclude that Bayer is *sui generis* in terms of brand longevity and familiarity. And there is no dispute that consumers generally rate familiar products or advertised products higher than others apart from use experience. And in 1975, users and nonusers alike rated Bayer higher in terms of effectiveness and speed, both of which are generic claims.

1333. Bayer Aspirin is another product with a long-standing, reliable position in the consumer's mind (perhaps even more so than Gerber's Baby Food) (Ross, Tr. 5880–81). Dr. Ross, however, totally ignored the familiarity or longevity factor in his evaluation of brand image data regarding plain 5–grain aspirins. *See also* F. 1237, *supra.*

1334. The record evidence is consistent with the view that, because of its unique longevity and brand familiarity, Bayer has always enjoyed a fairly high level of favorable product image (particularly with respect to such generic attributes as efficacy and safety) among users and nonusers alike and equally among those who have been exposed to or remembered any *unlawful* advertisements and those who have not. [**326**]

1335. In fact, of some fifty-two Bayer Aspirin advertisements found to be offensive, those containing the "faster acting" or "gentler" type of therapeutic claims numbered a scant dozen. The remainder contained claims of "best" or "world's best" aspirin, both bordering on puffery. *See* F. 293–294, 306–07, *supra.*

1336. There is also some evidence that the relatively small number of Bayer advertisements found to contain therapeutic claims did poorly in terms of related recall scores in copy tests, meaning that these advertisements were not effectively conveying the advertising messages to the audience. *See* RPF 5.204–5.212.

1337. From all of the foregoing, it is found that the record evidence is insufficient to show that respondent's unlawful advertisements played any significant role in creating or reinforcing a consumer image of therapeutic superiority for Bayer to the extent such image is found to exist in this record.

C. *The Record Does Not Show A Need For Corrective Advertising Regarding Bayer Aspirin*

1338. As discussed in B hereinabove, the record shows that in 1975 a substantial number of consumers had an image of Bayer Aspirin as being superior to other aspirins in terms of effectiveness and speed. However, the record evidence is insufficient to show that Bayer's superiority image, to the extent it existed in 1975, was attributable in any significant respect to respondent's advertising claims of

Bayer's therapeutic superiority. Furthermore, in view of the relatively small number of advertisements containing therapeutic superiority claims, disseminated during a relatively short period of time almost a decade ago, an inference that such image, to the extent, if any, attributable to the offending Bayer advertising, is likely to persist into the 1980's in the absence of such advertising since the middle 70's is not reasonable. *See* F. 1335.

1339. Recent research regarding corrective advertising has shown that the fashioning of a corrective message is a very difficult task. A message which appears acceptable can sometimes convey to consumers meaning beyond or outside what was intended by the author (*See* RPF 6.318–6.320). In this case, the problem is compounded by the need not to inhibit dissemination of advertising information containing true and unmisleading claims of product quality, including comparative claims where appropriate. Since the record evidence is insufficient to support an inference that there is an image [**327**] attributable to unlawful advertising claims with respect to Bayer, the justification for any corrective advertising involving Bayer is lacking in this record.

1340. Furthermore, the effect of a corrective advertising order regarding Bayer Aspirin may be to injure all 5–grain aspirins on the market. Bayer Aspirin is the only product which advertises for aspirin *per se* and which defends aspirin as a generic category against the antiaspirin advertising of the combination and acetaminophen products. Bayer is identified with the generic class of straight aspirin. A corrective statement or a disclaimer statement would weaken any Bayer advertising and would be likely to injure all straight aspirin products (Miles, Tr. 9464).

1341. Corrective advertising would be likely to be punitive as against Bayer Aspirin, in that its effect would not be limited to correcting an alleged incorrect belief but would injure the product's image and position generally, including product attributes the correctness of which is not questioned (Miles, Tr. 9436).

1342. Corrective advertising for Bayer Aspirin would be harmful because the basic image of Bayer Aspirin is that of old fashioned, reliable high-quality, which rests in substantial part on a stock of goodwill. As the "grandfather brand" it has been building this goodwill for more than 50 years. Once lost, Bayer's goodwill would be practically impossible to retrieve (Miles, Tr. 9463).

X. RESPONDENT LOIS HOLLAND CALLAWAY IS LIABLE FOR ITS CREATING AND DISSEMINATING CERTAIN CHALLENGED ADVERTISING CLAIMS

1343. Respondent Lois Holland Callaway, Inc. ("LHC") actively participated in the creation and dissemination of all challenged Van-

quish advertisements disseminated after April 1971. That participation included development of Vanquish advertising copy strategies, and development jointly with Sterling's Glenbrook Laboratories Division of Vanquish marketing plans, beginning with the 1972 marketing plan (CX 678, admission 225; CX 681, admission 268).

1344. LHC played a substantial role as Sterling's advertising agency for the development of the following advertisements for Vanquish between April 1971 and 1974: CX 252–256 and 258–264 (CX 632A, B). These advertisements were disseminated from May 1971 to December 1974 (CX 632A, B), and made all representations as alleged in Complaint Paragraph 8(B)(2), 8(C), 12(B)(1), 12(B)(2), 12(C) and failed to disclose the presence of aspirin as alleged in Complaint Paragraph 23. **[328]**

1345. Through CX 252–256 and 258–264 LHC represented that a recommended dose of Vanquish is more effective for the relief of pain than a recommended dose of aspirin or buffered aspirin, and that this comparative superiority is established. Through CX 252, 253, 255, 256, 258–264 LHC represented that a recommended dose of Vanquish is more effective for relief of pain than the largest "extra strength" tablet, and that this comparative superiority is established. Through CX 252–256 and 258–264 LHC represented that because Vanquish contains "gentle buffers" it will result in less gastric discomfort than any internal analgesic not containing buffers, and that this comparative superiority is established. Throughout CX 252–256 and 258–264 LHC failed to disclose that Vanquish contains aspirin.

1346. With respect to comparative efficacy and safety claims regarding Vanquish, the record indicates that there were some literature and research support for those propositions at the time these claims were disseminated, although they had not been convincingly demonstrated by well-controlled clinical studies. In these circumstances, it was reasonable for LHC to have relied on its client's scientific judgment in favor of these claims, based in part on Sterling's in-house research data. The record does not show that LHC in fact knew of any cogent scientific evidence to contradict its client's scientific judgment in this regard. The view that Section 5 requires an advertising agency to conduct its own study or to obtain independent scientific opinion in order to verify the scientific validity of proposed advertising claims is rejected.

DISCUSSION

A. *Introduction*

The instant proceeding (D. 8919) is one of the three related OTC internal analgesic advertising cases instituted by the FTC in February 1973 under Sections 5 and 12 of the FTC Act. An Initial Decision has been filed in each of the other two cases, *i.e., Bristol-Myers Co., et al.,* (D. 8917), September 28, 1979 [102 F.T.C. 21 (1983)]; *American Home Products Corp., et al.,* (D. 8918), September 1, 1978 [98 F.T.C. 136 (1981)]. D. 8917 (*Bristol-Myers*) involved certain advertising claims for Bufferin (a buffered aspirin product), Excedrin (a combination aspirin product also containing acetaminophen, salicylamide and caffeine) and Excedrin P.M. (a combination aspirin product also containing acetaminophen, salicylamide and methapyrilene fumarate). D. 8918 (*American Home Products*) involved certain advertising claims for Anacin (an aspirin-caffeine combination product) and Arthritis Pain Formula (a buffered aspirin product). D. 8917 (*Sterling Drug*) involves Bayer Aspirin (plain 5-grain aspirin tablets), Bayer Children's Aspirin (plain aspirin tablets for children), Cope (a buffered **[329]** combination aspirin product also containing caffeine and methapyrilene fumarate), Vanquish (a buffered aspirin product also containing caffeine and acetaminophen) and Midol (a combination aspirin product also containing caffeine and cinnamedrine HCL). Joint hearings in the three cases were held in June, July and August of 1977, followed by further separate hearings in each of the three cases.

Although the three advertising cases involved various OTC analgesic products of different formulations, they have certain common core issues of law and fact, namely, the appropriate legal standards governing the advertising claims of simple or comparative efficacy and/or safety found to have been made for the various OTC analgesic products and the adequacy of medical-scientific evidence the advertiser relied on as substantiation of its advertising claims.

In this Initial Decision, the ALJ has attempted to follow the same legal standards articulated in the earlier cases in light of the evidence contained in this record and endeavored to fashion self-explanatory findings. Therefore, the discussion which follows will be limited to certain key issues which are unique to this case. Among such issues are (1) comparative advertising claims of drug product quality (or pharmaceutical quality) as distinguished from implied efficacy or safety claims, (2) the reasonable basis required for a comparative pharmaceutical quality claim, (3) physicochemical evidence and blood level data as bases for superior therapeutic claims regarding plain

5–grain aspirins, (4) Section 5 liability for the so-called inconsistent claims, and (5) the propriety of corrective advertising requirement with respect to Bayer Aspirin.

B. *Consumers Recognize Pharmaceutical Quality As A Distinct Attribute Apart From Therapeutic Performance Of Drug Products Although The Two Are Ultimately Related*

Complaint counsel argue that an express claim that Bayer Aspirin has superior pharmaceutical quality over other USP aspirins in certain respects is an implied comparative therapeutic claim because consumers will perceive such a claim to mean that Bayer Aspirin's therapeutic performance is significantly superior to that of other aspirin brands. Thus, complaint counsel lump drug product quality claims (or pharmaceutical claims) and therapeutic claims (or medical claims) together and refuse to distinguish between an advertising claim that Bayer Aspirin is "faster" or "safer" than other aspirins and a claim that Bayer Aspirin is "a better **[330]** quality aspirin one can count on," or "a product that will do what aspirin tablets are supposed to do."[7]

Complaint counsel's argument is deficient in several important respects. *First,* it is clear from common sense and daily experience that drug product quality or pharmaceutical quality is a familiar concept which is readily recognized and understood as such by consumers apart from drug performance or efficacy. It is beyond dispute that consumers understand and desire drug product quality not necessarily because they believe that drug quality can affect the performance of a drug but primarily because they want quality, purity or freshness in a drug product for its own sake.[8] The fact that drug product quality can ultimately affect the therapeutic performance is not a good reason to ignore, in the guise of consumer protection, an important concept consumers recognize and on which they base their purchasing decisions in their daily lives.

Secondly, the inevitable and regretable consequence of complaint counsel's position will be to inhibit free and unfettered dissemination of true and nonmisleading information regarding significant drug quality improvements. Such a position would not only run counter to the Commission's established policy of encouraging free flow of important product information (*e.g., The Eyeglasses Industry Rulemaking Proceeding; The American Medical Association* (D. 9064)) but also may

[7] The ALJ recognizes that certain claims are comparative therapeutic claims even though they may be couched in terms of physicochemical or pharmaceutical terms. For example, a claim of superior dissolution speed is a comparative therapeutic claim because the speed of aspirin tablet dissolution can have no independent meaning apart from speed of pain relief action to consumers.

[8] *See, generally,* Professor Boulding's thoughtful presidential lecture at the American Association for Advancement of Science annual meeting in January 1980. Kenneth E. Boulding, "Science: Our Common Heritage," *Science,* 207:831–836 (1980).

have such a chilling effect as to constitute an unreasonable prior restraint on legitimate commercial speech protected by the First Amendment.[9] **[331]**

Finally, since there is no dispute that public policy should encourage improvement of the pharmaceutical quality of drug products, complaint counsel's technical interpretation of drug quality advertising claims would reduce incentives for drug quality improvements and thus be counterproductive while having no significant redeeming features.[10]

C. *An Affirmative Product Claim Must Be Based On A Reasonable Basis And With Respect To A Drug Product Quality Claim Based On Physicochemical Studies, Such Studies Must Show Statistically And Clinically Significant Difference*

It is now well-established that an affirmative product claim must be based on a reasonable basis at the time such a claim is made and that certain advertising claims must be adequately supported by appropriate scientific evidence. *Pfizer, Inc.,* 81 F.T.C. 23 (1972); *Firestone Tire & Rubber Co.,* 81 F.T.C. 398 (1972), *aff'd,* 481 F.2d 246 (6th Cir. 1973), *cert. denied,* 414 U.S. 1122 (1973); *National Dynamics,* 82 F.T.C. 398 (1972), *aff'd,* 492 F.2d 1333 (2d Cir. 1973), *cert. denied,* 419 U.S. 993 (1974). **[332]**

A claim that Bayer Aspirin is superior in quality to other aspirin brands implies that the claim is supported by appropriate scientific evidence. Sterling's express reliance on scientific tests in its Blue Book advertising campaign shows Sterling's acceptance of that substantiation requirement. Indeed, in this proceeding Sterling's first-line defense with respect to the challenged Bayer advertising claims is that there was adequate scientific substantiation for the pharmaceutical claims it made. Reason and common sense require that, to the extent aspirin quality claims are based on physicochemical comparisons, such studies be of a sound design consonant with recog-

[9] *Va. State Board of Pharmacy* v. *Va. Citizens Consumer Counsel, Inc.,* 425 U.S. 748 (1976); *Bates* v. *State Bar of Ariz.,* 433 U.S. 350 (1977); *Central Hudson Gas & Elec. Corp.* v. *Public Serv. Commission,* 100 S.Ct. 2343 (1980). *Also see* Tribe, *American Constitutional Law,* at 651–56, 712–14, 721–24, 728–30 (1978).

[10] The ALJ recognizes the close questions of policy involving certain competing considerations which demand a careful deliberation regarding Bayer's superior quality claims. *First,* Section 5 of the FTC Act mandates the Commission to prevent deceptive, or confusing or spurious therapeutic superiority claims based on insignificant physicochemical differences which are capable of misleading consumers. *Second,* it is an important, recognized public policy objective to promote the improvement of drug product quality, and a requirement that every pharmaceutical claim which may be said to convey a therapeutic message to some consumers be supported by well-controlled clinical trials may run counter to the policy of encouraging all improvements in drug product quality independent of their therapeutic importance. *Third,* a legal requirement that every comparative pharmaceutical quality claim be substantiated by well-controlled clinical trials may have a chilling effect upon true and honest claims of product quality, and be tantamount to unlawful prior restraint on commercial speech. Finally, it may run counter to the Commission's established policy of encouraging free flow of significant product information.

After due deliberation, the ALJ is of the opinion that the resolution reached herein is reasonable and realistic in light of the record as a whole.

nized scientific design principles and the results show statistically significant differences. This is essential in order to insure that the results of such studies do reflect a true difference and are not a result of chance. Furthermore, with respect to a drug quality claim, mere statistical significance in terms of some physicochemical characteristics could be meaningless unless it is also clinically significant, not in the sense that the superiority of one aspirin has been demonstrated through clinical studies but in the sense that the difference observed can reasonably be expected to (or is known to) have a significant clinical impact in the opinion of biomedical experts.

On the other hand, if advertisers were allowed to claim superior drug quality for their products without adequate medical-scientific substantiation outlined above, consumers will be hopelessly confused and misled by claims of differences which are, in reality, illusory or meaningless. The result would not only be unfair to consumers but also to other competitors who do not make drug quality claims unless they do have appropriate medical-scientific substantiation.

D. *The Record Evidence Regarding The Physicochemical Characteristics Of Bayer Is Insufficient To Substantiate Therapeutic Superiority Claims Of Bayer*

During the trial, Sterling advanced a position which would apply different standards of substantiation to comparative therapeutic claims for buffered or combination aspirin products, on the one hand, and to similar claims for plain 5-grain aspirin, on the other hand. With respect to the former, Sterling would require well-controlled clinical studies. As to the latter, Sterling argues that the record evidence regarding physicochemical characteristics of Bayer and other brands constitutes adequate substantiation of comparative therapeutic claims for Bayer. This argument is rejected for several reasons.

First, the record as a whole is persuasive that a comparative therapeutic claim of one brand of plain 5-grain aspirin over another USP 5-grain aspirin based solely on [333] physicochemical differences remains an hypothesis to be clinically tested although the hypothesis does appear rational and plausible in terms of recognized pharmaceutical and pharmacological principles. Until so tested and confirmed, the superiority claim stands unsubstantiated.

The record is clear that since the early 1960's there has been little dispute in the biomedical scientific community that the efficacy of drugs must be demonstrated by well-controlled clinical studies, including appropriate replication. This basic principle was applied equally to new therapeutic agents and to new formulations of drugs recognized as effective. The record shows that until this trial Sterling has subscribed to this view in various representations made to the

FTC and the FDA. In recent years, a vocal dissent from that position has been heard. There are respected scientists who sincerely believe that the strict FDA requirements regarding clinical trials have exacted excessive costs in terms of delayed introduction of important new drugs as well as in terms of research and economic resources. They urge that other less costly alternatives short of well-controlled clinical studies should be accepted. However, the record shows that this remains a minority view in this country.

In any event, reason and common sense argue that the need for clinical demonstration becomes more acute when the claim is not of simple efficacy but is that one brand of plain 5–grain aspirin is therapeutically superior to other USP aspirins. There appears to be a paucity of reports of clinical studies comparing different brands of plain 5–grain aspirin. A possible explanation of this fact may be that biomedical scientists believe, as a basic proposition, that generic equivalents (such as different brands of plain 5–grain aspirin) are therapeutic equivalents until the contrary is shown to be the case. It is reasonable and fair that those who claim therapeutic superiority of one brand of drug product over another generically equivalent product demonstrate the therapeutic superiority of their product through well-controlled clinical trials. Until this has been done, such therapeutic superiority claims remain unsubstantiated, and physicochemical data alone are insufficient to fill the fundamental gap.

In defense of Bayer's therapeutic superiority, Sterling placed a heavy reliance upon research literature related to biopharmaceutical and dissolution rate-time characteristics of drug products, and vigorously argued that pharmaceutical equivalents are not therapeutic equivalents. However, the record is clear that the only time bioavailability can significantly affect aspirin's therapeutic performance is when aspirin is administered in chronically high-level maintenance doses for the treatment of rheumatoid arthritis or rheumatic fever, an area found to be inappropriate for self-medication by the FDA-OTC Internal Analgesics Panel (CX 466). The research **[334]** and review articles Sterling relies on make clear that the "truth of the matter is that although drug formulations has been studied extensively *in vitro,* the clinical significance and the extent of generic inequivalence is unknown." "[D]rug activity is not necessarily related to drug concentrations in plasma. In addition, the plasma concentration of a drug depends not only on absorption, but also on individual characteristics and kinetics of drug distribution, methabolism and excretion" (RX 250-Prescott, at 287, 289). The same author concluded:

> The incidence and ultimate clinical significance of generic inequivalence is unknown .... [I]t is clear that complex *in vitro* studies of drug formulations cannot be relied on

to predict the performance of drugs in clinical practice. . . . There is an appalling lack of information on the equivalence of drugs in the very situation where it is most needed—in patients with diseases.

In 1972, in concluding a 40–page review article of tableting research and technology, a recognized pharmaceutical expert cautioned that "[i]n spite of increasing activity at the biological level [publication of research papers], the investigational gap in *in vitro - in vivo* correlations involving the tablet dosage form remains too wide" (RX 250-Cooper, at 1531, 1550). The record shows that these observations still hold true today. The record is convincing that evidence other than well-controlled clinical studies are insufficient to provide a reasonable basis for a comparative therapeutic proposition regarding plain 5–grain aspirin brands, which are generic equivalents.

Sterling's argument that conducting costly, large-scale clinical trials of different brands of plain 5–grain aspirin are fraught with many difficulties and that this is not an optimal utilization of biomedical research resources has considerable force. In the final analysis, however, there are no insurmountable ethical or logistic barriers to conducting well-controlled clinical studies of a relatively small number of leading brands of plain 5–grain aspirin. If Sterling insists on advertising therapeutic superiority claims for Bayer, Sterling should conduct the required clinical studies. On the other hand, it may well be that, because of the present state of art in analgesometry, whatever therapeutic differences that may exist among different brands of plain 5–grain aspirin may not be large enough to be observed or to reach statistical and clinical significance. Should this be the case, then Sterling would be put in no different position than its competitors with regard to their comparative therapeutic claims for OTC analgesic products. Furthermore, there is nothing to suggest that consumers make a distinction in terms of the kind and degree of scientific substantiation they expect with respect to therapeutic superiority claims for combination products, on the [335] one hand, and similar claims for plain 5–grain aspirin, on the other hand. For plain aspirins and combination products alike, a therapeutic superiority claim stands unsubstantiated until it is demonstrated by well-controlled clinical studies.

Sterling's argument that the FDA instructed the various OTC drug monograph panels, including the OTC Internal Analgesics Panel, that they may base conclusions regarding the effectiveness of OTC drugs under review solely upon data other than well-controlled clinical trials is not persuasive (RPF 7.879–7.891). In the administrative law judge's view, the most that can be inferred from the information Sterling relies on in this regard, is that (1) the FDA intended the OTC

drug monograph panels to consider all available scientific information, including data other than well-controlled clinical studies, and (2) the FDA intended to permit the panels to reach conclusions regarding the effectiveness of OTC drug ingredients under review, even in the absence of well-controlled clinical studies, on the basis of the available data. This is a far cry from saying that the FDA no longer requires well-controlled clinical trials in support of drug efficacy or that the FDA is willing to settle for something less than controlled clinical demonstration in all cases. Suffice it to say the record is devoid of any evidence to show that the FDA has approved an NDA involving any analgesic agent without the required clinical demonstration.

Second, in any event, the inference that can be drawn from physicochemical data regarding aspirin tablets is often a matter of degree and cannot provide a clearcut or definitive conclusion regarding the relative therapeutic performance of different brands being compared. There is no dispute that some physicochemical characteristics of aspirin tablets (such as dissolution profile) are expected to have a greater bearing on the tablet's therapeutic performance than other characteristics, or that some of the desirable physicochemical factors are mutually antagonistic in the sense that one may be enhanced at the expense of some others. Therefore, even in cases where statistically significant differences in some physicochemical characteristics are shown, the final, all important question of whether such differences in themselves are sufficient to make a significant therapeutic impact in actual use can only be resolved by well-controlled clinical tests. The assertion that, other things being equal, an aspirin brand which is better than another brand in terms of one or more physicochemical factors is preferable and that this "clinical" judgment requires no well-controlled clinical trials merely begs the question.

Finally, the various physicochemical evidence and non-clinical *in vivo* data (such as blood level data) Sterling relies on are equivocal or inconclusive. The various physicochemical studies suffer from significant deficiencies in design, execution and/or analysis, or fail to show statistical significance. Also, blood level data do not provide a reliable **[336]** answer to the question of comparative efficacy of aspirins because, as Sterling agrees, a precise correlation between the blood salicylate level and either the onset, duration or intensity of analgesia is yet to be established.

E. *Section 5 Liability Based On Inconsistent Advertising Claims Is Not Only Vague But May Constitute Unlawful Prior Restraint Upon Commercial Speech*

Complaint counsel argue that Sterling's contemporaneous dissemination of mutually inconsistent advertising claims regarding differ-

ent analgesic products it marketed is a violation of Section 5 not only because mutually inconsistent or conflicting claims regarding these products cannot be true at the same time, but also because they are unfair to consumers. This is a novel theory. Although this theory has some surface plausibility, it raises serious constitutional problems as it has been presented in this case.

First, the standard of consistent claims is not clearly articulated, nor is its content defined with sufficient clarity. Vague legal requirements accompanied by sanction are not consistent with due process.[11] *Secondly,* what is an advertiser to do when advertising claims for different products have equally reasonable basis although some of the claims may arguably not be consistent with some others? Should the advertiser forego some advertising claims having reasonable basis or make the claims at its peril? One thing is clear in these circumstances. The "consistency" requirement would have a chilling effect and may amount to an unreasonable restraint upon legitimate commercial speech in contravention of the First Amendment. For all of these reasons, complaint counsel's "inconsistent claims" theory is rejected.

F. *The Evidence Is Insufficient To Support A Corrective Advertising Requirement With Respect To Bayer Aspirin*

The basic rationale of the corrective advertising requirement in Section 5 cases is that because of the intensity and duration of the dissemination of unlawful advertising claims it may be reasonably inferred (1) that the offending advertising claims played a significant role in creating or reinforcing a mistaken product image and (2) that in the absence of a corrective advertising the mistaken product image will endure for a significant period of time. In my view, the record [337] evidence is insufficient to support either of the two necessary elements outlined above.

First, as detailed in F. 293–94, 314, 1335, *supra,* I have found that the number of offending Bayer Aspirin advertising in evidence is relatively small.[12] According to CX 630, these offending TV ads were run intermittently during a relatively short period of time, at some period between January 1969 and March 1973. Furthermore, although these advertisements were found to have implied a therapeutic claim, they were not like the more blatant comparative efficacy claims that Sterling made for Vanquish, for example, or those comparative claims made by some of Sterling's competitors.

Secondly, the record evidence is consistent with the view that Bay-

[11] *See* Tribe, n. 9, *supra,* at 718–720.

[12] Of some fifty odd Bayer Aspirin advertisements found to be offensive, those containing the more familiar "faster acting" or "gentler" claim numbered a scant dozen during the 1967–1973 period. The remaining ads were found offensive because they contained claims of "best" or "world's best" aspirin, both bordering on puffery. F. 293–294, *supra.*

er's relatively high therapeutic image is due to Bayer's unique longevity and brand familiarity among consumers. F. 1320–34, *supra.* In these circumstances, it is not reasonable to infer that Sterling's offending advertising played a significant role in creating or reinforcing Bayer's superiority image and to require Bayer to include a corrective advertising message in all future Bayer advertisements.

In sum, the administrative law judge is persuaded that the record evidence does not support a corrective advertising remedy with respect to Bayer. Corrective advertising is an equitable remedy and should be required only when there is convincing evidence showing its need. In the administrative law judge's opinion, this is not such a case.[13]

G. *Liability Of Lois Holland Callaway*

The law is well-settled that an advertising agency may be held liable for false advertising if it "actually participated in the deception ... In order to be held a participant in such [**338**] deception, the agency must know or have reason to know of the falsity of the advertising." *Doherty, Clifford, Steers and Shenfield, Inc.* v. *FTC,* 392 F.2d 921, 918 (6th Cir. 1968); also *Carter Products, Inc.* v. *FTC,* 323 F.2d 523, 534 (5th Cir. 1963); *ITT Continental Baking Co., Inc.,* 83 F.T.C. 865 (1973).

In determining liability, the agency will be strictly held to know what claims are made in advertisements. *In re Merck & Co.,* 69 F.T.C. 526, 559 (1966), *aff'd,* 392 F.2d 921 (6th Cir. 1968). *ITT Continental, supra.* Since LHC actively participated in the creation and dissemination of the challenged advertisements for Vanquish, the remaining issues regarding its liability is whether it knew or should have known that the advertisements were false due to failure to disclose material facts of the presence of aspirin and the existence of a substantial question in the medical scientific community concerning the validity of the "establishment" claims regarding Vanquish.

Complaint counsel argue that respondent's absolute and comparative efficacy (and related) claims for Vanquish were false because, having represented these claims as being "established" by scientific evidence, LHC knew or should have known that the data supporting the claims were subject to "substantial question" among experts and that the existence of such substantial question was a material fact which should have been disclosed to consumers. Complaint counsel also argue that the failure to disclose the presence of aspirin in Vanquish was false because LHC knew, or should have known, that since

[13] In *Warner-Lambert,* the cold-preventive image of Listerine was shown to be about three times as high as that of competitive products. 86 F.T.C. at 1503. Also in this connection, Professor Emerson's reminder bears repeating today in the context of this case. We should be ever mindful of the danger of imposing restrictive rules which may be valid in principle but may tend in actual operation to circumscribe freedom of expression. Emerson, "Toward A General Theory of the First Amendment," 72 Yale L.J. 877, 901–902 (1963).

aspirin may cause undesirable side effects in certain users, implicit promotion of these analgesics as containing ingredients other than aspirin and failure to disclose the presence of aspirin was false advertising by virtue of the fact that the presence of aspirin is material fact knowledge of which may cause some consumers to change their purchase decisions.

It is my determination that the record as a whole supports the conclusion that LHC's good faith reliance on Sterling's substantiation information with respect to the comparative efficacy claims for Vanquish was reasonable under the circumstances.

With respect to advertising agency's liability under the establishment/substantial question theory, it is my determination that the same standards applicable to drug manufacturing firms are not appropriate for advertising agencies. Here, as in my Initial Decision in *American Home Products,* Docket No. 8918, dated September 1, 1978 (p. 225) [98 F.T.C. at 340 (1981)], LHC is found to have acted reasonably in relying in good faith on the substantiation data provided by Sterling. As the record in this case amply demonstrates, scientific analysis or verification of the accuracy of clinical data is a highly complex, technical process, one for which LHC is not, and may **[339]** not reasonably be expected to be, equipped. Even where complaint counsel have shown the advertising agency to have been aware of some questions concerning the validity of its unqualified representations, LHC was not obligated to perform statistical or clinical analyses of the representations to determine the "substantiality" of the question or its "materiality." I reiterate my conclusions in *American Home Products:*

> This is not a case where the disparity between the advertising representations and the substantiation information is so great as to preclude a conclusion that the advertisements were conceived through reasonable reliance on the assurances of the manufacturer that the claim is true or has a reasonable basis. *Cf. Standard Oil Co. of California,* 84 F.T.C. 1401, 1474–75 (1974). Clyne [advertising agency] cannot be reasonably charged with the duty to conduct an independent investigation that the claim is scientifically established in the sense that there existed two or more well-controlled clinical demonstrations in support of the claim. In these circumstances. Clyne's good faith reliance on American Home's assurances, as embodied in CX 304, was reasonable.

H. *Relief*

It is well-established that in Section 5 cases the Commission has the power and duty to fashion appropriate remedies which are reasonably calculated to prohibit the unlawful practices found to exist. *E.g., Jacob Siegel Co.* v. *FTC,* 327 U.S. 608, 611–13 (1946); *FTC* v. *Ruberoid Co.,* 343 U.S. 470, 473 (1952); *FTC* v. *National Lead Co.,* 352 U.S. 419, 428–30 (1957). The remedy must have a reasonable relationship to the

unlawful practice and be no broader than is reasonably necessary to remedy the violation. *Jacob Siegel Co.* v. *FTC, supra,* at 613; *Beneficial Corp.* v. *FTC,* 542 F.2d 611, 619–20 (3d Cir. 1976). *See also Warner-Lambert Co.* v. *FTC,* 562 F.2d 749, 757–58 (D.C. Cir. 1977); *National Commission on Egg Nutrition* v. *FTC,* 570 F.2d 157, 164 (7th Cir. 1977).

1. Part I Of The Order

Part I of the Order would prohibit simple and noncomparative efficacy or safety claims that are not supported by a reasonable basis. The provision is justified by Sterling's failure to have a reasonable basis for various tension and depression relief claims for Bayer, Cope and Midol and by Sterling's failure to possess and rely on a reasonable basis for its superiority claims for Bayer and BCA, Vanquish and Cope. [340] Reasonable basis is defined to be "competent and reliable scientific evidence" for both simple and comparative effectiveness claims; however, as to comparative (therapeutic superiority) claims regarding OTC analgesic products, reasonable basis is further specified to be the well-controlled clinical evidence described in Part II(E). This further explication of reasonable basis standards for comparative claims involving a particular product class is based upon the extensive record evidence on the kind of data necessary to provide reasonable scientific support for such claims.

Inclusion of all OTC drug products in the reasonable basis requirement provision is appropriate in this case. Sterling appears to have been involved in a number of Section 5 proceedings which resulted in cease and desist orders or consent orders involving misrepresentation of a number of OTC drug products.[14] It is now time to place Sterling under a broad proscription with respect to all OTC drug products marketed by it. Furthermore, the proscription here is narrow and related to the particular type of claims involved in this case.

2. Part II Of The Order

Part II(A) prohibits any claim that an ingredient or combination of ingredients is unusual, special or exclusive when that ingredient or combination is available in other [341] analgesics. This is based upon

[14] Sterling has five outstanding advertising orders against it, four by consent and one after litigation. In a 1950 litigated order, Sterling was ordered to cease representing that Phillips Milk of Magnesia Skin Cream and Cleansing Cream was effective for keeping the skin free of enlarged pores and would control oiliness and from misrepresenting the benefits of these products. Sterling agreed not to represent Camphophenique, an antiseptic, as an effective cure for pimples, acne, skin rashes or as effective treatment for insect bites. 49 F.T.C. 1635 (1953). In a 1962 consent agreement, Sterling agreed to cease representing that Isuprel or similar drugs had no adverse side effects and could be taken without risk of toxic side effects. 61 F.T.C. 1008 (1962). In a 1968 consent agreement, Sterling agreed not to misrepresent the benefits of Ironized Yeast Tablets as a remedy for weakness, tiredness, frequent headaches, nervousness, loss of appetite, loss of energy or restlessness. 73 F.T.C. 979 (1968). Most recently, in a 1974 consent agreement, Sterling agreed not to represent that Lysol or any other household disinfectant will be of benefit in reducing the incidence or spread of influenza or throat infections and not to overstate the value of such disinfectants against strep and staph infections. 84 F.T.C. 547 (1974).

respondent's unfair and deceptive claims of the uniqueness of Cope's formula (Complaint Paragraph 22).

Part II(B) prohibits respondent from misrepresenting the identity of commonly known ingredients in its advertising, as the record shows they have done here, by falsely representing that these ingredients were something other than commonly known aspirin and caffeine (Complaint Paragraph 26).

Part II(C) requires respondent to disclose the presence of aspirin in every OTC drug product it advertises. The provision is based upon the record evidence which demonstrates that the presence of aspirin is a material fact which, if known to consumers, might influence their decision to purchase the drug. The provision is also justified by respondents' uniform, continuous advertising representations that have the tendency and capacity to lead consumers to believe that aspirin is not an ingredient in Midol (Complaint Paragraphs 24–25).

Part II(D) of the Order prohibits respondent from misrepresenting the results or analysis of any test, study or survey. The provision is based upon the misrepresentation of the results of the tests for Bayer and Cope challenged in Paragraphs 18 through 21 of the Complaint. The additional coverage extending to studies and surveys is justified because the technique abused in the representations challenged here is equally applicable to any study or survey.

Part II(E) of the Order prohibits representations that comparative effectiveness or comparative freedom from side effects of any OTC internal analgesic product has been established unless such is, in fact, the case. The requirements which must be met before an "established" claim can be made are based primarily on FDA's regulations, which set forth the criteria for "adequate and well-controlled" clinical investigations necessary to provide "substantial evidence" of effectiveness for new drugs (21 C.F.R. 311.111(a)(5)(ii)), and which have also been applied to OTC drugs (21 C.F.R. 330.10(a)(4)(ii)). *See* F. 449, *supra;* CB at 127–34. The FDA regulations have been modified for purposes of this Order in certain limited respects in light of the fact (1) comparative efficacy and comparative freedom from side effects are involved in this section of the Order and (2) only OTC internal analgesic drugs are involved.

Among the modifications are the following:

Part II(E) of the Order requires "*two or more* adequate and well-controlled clinical investigations conducted by *independent* experts . . ." The underlined portions have been added to the requirements of the FDA regulation to make it explicit that at least two studies must be conducted, and that the studies should [342] be done by different researchers. The language is virtually identical to the FDA Analgesic

Panel's conclusion that a Category III compound can achieve Category I status only on the basis of "at least two studies by independent investigators which conform to the guidelines [for well-controlled studies]" (CX 466 at 35445).

Since both comparative efficacy and comparative freedom from side effects are addressed in Part II(E), the FDA requirements have also been modified to reflect that fact. For example, the order provision requires that experts must conclude on the basis of the clinical studies that "the drug will have the comparative effectiveness or comparative freedom from side effects it is represented to have . . ." In addition, the Order contains a requirement, not found in the FDA regulation, that the "comparative effectiveness or comparative freedom from side effects [be] demonstrated by methods of statistical significance, and with levels of confidence, that are generally required by . . . experts." Such a requirement is necessary in light of the expert testimony in this record which demonstrated the need for statistically significant differences between drugs before any firm conclusions could be reached concerning comparative efficacy or side effects.

Part II(E), unlike the FDA regulation, requires that:

> [a]t least one of the . . . investigations to evaluate the comparative effectiveness of the drug shall be conducted on any disease or condition referred to, directly or by implication [in advertising]; or, if no specific disease is referred to, then the . . . investigations shall be conducted on at least two conditions or diseases for which the drug is effective.[15]

In other words, if a claim is made that one of respondent's OTC drugs is superior for a certain condition (*e.g.,* headache) to another product, at least one of the two studies *must* be on that particular condition. On the other hand, if a "general" superior efficacy claim is made, *e.g.,* "Vanquish is a more effective pain reliever than Drug X," the studies must show superiority in at least two conditions "for which [Vanquish] is **[343]** effective," such as headache pain and post-partum pain. Part II(E) is designed to insure that the covered superiority claims are not made with respect to a type of pain or condition for which superiority has not been demonstrated. Likewise, it is designed to preclude general claims of superiority based on studies conducted on conditions for which OTC drugs are not generally used.

Finally, Part II(E) of the Proposed Order requires that the studies be double-blind and placebo-controlled, even though the FDA regulation does not contain an explicit requirement for such controls. The regulation does indicate, however, that a placebo should be used ex-

[15] This portion of Part II does not apply to claims relating to comparative freedom from side effects. In other words, respondent could test its drug on healthy volunteers, who have no "condition or disease," and establish that its drug causes less gastric upset.

cept in circumstances where (1) "objective measurements of effectiveness are available and placebo effect is negligible," (2) the condition treated is such that administration of a placebo would be contrary to the interest of the patient," or (3) a drug is studied on "diseases with high and predictable mortality . . ." (21 C.F.R. 314.111(a)(5)(ii)(a)(4)(i) through (iv)). None of those situations is applicable to studies involving the comparative performance of OTC drugs, and for this reason a placebo control should be required in the Order. Likewise, even though the FDA regulation does not specify that all efficacy studies must be conducted under double-blind conditions—presumably because such a condition would be impossible or unethical when certain types of drugs were studied (*e.g.,* chemotherapeutic drugs)—it did require that the study must be designed to "minimize bias on the part of the subject and observer." It is my view that comparative analgesic studies should be double-blind to the extent possible.

Part II(F) of the Order prohibits respondent from making comparative effectiveness or comparative freedom from side effects claims in the face of a substantial question unless the existence of that substantial question is disclosed. It, thus, is directly related to two of the most basic allegations of lawfulness in this case, the unfairness of making comparative claims for drugs in the face of a substantial question and the misleading nature of advertisements which fail to disclose the material fact that there exists a substantial question concerning the validity of a comparative claim. The requirements of Part II(F) do not apply unless they are "triggered" by respondent's choice to make a comparative therapeutic claim.

3. Part III Of The Order

Part III of the Order is designed to implement the requirement that any comparative drug product quality claim or pharmaceutical claim be appropriately supported by a sound scientific study conducted by experts or other qualified personnel which show statistical and clinical significance of the physicochemical differences observed. This section is necessary because Sterling made superior quality claims without [**344**] a reasonable basis as alleged in Complaint Paragraphs Twenty and Twenty-One. This section would also limit the requirements as to statistical analysis to quality factors which can be quantified by generally accepted or appropriate procedures.

4. Part IV Of The Order

Part IV of the Order is directed to LHC, the advertising agency for Vanquish, and requires LHC to refrain from making certain advertising claims or failing to disclose a material fact with respect to nonprescription internal analgesic products containing aspirin.

Conclusions of Law

1. The Federal Trade Commission has jurisdiction over the advertising of Bayer Aspirin, Bayer Children Aspirin, Midol, Cope and Vanquish under Section 5 of the Federal Trade Commission Act.

2. Each of the various charges of the Complaint has been sustained by a preponderance of credible evidence, except with respect to Complaint Paragraph Twenty-Nine insofar as it relates to Complaint Paragraph Seventeen. Respondents' use of false, misleading and deceptive representations as herein found has had and now has the capacity and tendency to mislead members of the purchasing public into the erroneous and mistaken belief that said statements and representations were and are true and into the purchase of substantial quantities of Bayer Aspirin, Bayer Children Aspirin, Midol, Cope and Vanquish by reason of this erroneous and mistaken belief. In the absence of an appropriate cease and desist order, including appropriate affirmative disclosure requirements, consumers will continue to be misled by respondents' advertising representations regarding efficacy or safety or quality of said products that such representations are supported by scientific evidence generally accepted by the scientific community as establishing such propositions or have adequate substantiation.

3. The acts and practices of respondents as herein found were and are prejudicial and injurious to the public and to respondents' competitors and constituted and now constitute unfair methods of competition and unfair and deceptive acts and practices in commerce in violation of Sections 5 and 12 of the Federal Trade Commission Act.

4. The accompanying order is necessary and appropriate for the purpose of prohibiting the continuation of the proscribed acts and remedying the injury and unfairness to the consuming public. **[345]**

Order

I.

It is ordered, That respondent Sterling Drug, Inc., a corporation, its successors and assigns, and respondent's officers, agents, representatives and employees directly or through any corporation, subsidiary, division or other device, in connection with the labeling, advertising, offering for sale, sale or distribution of any nonprescription drug in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from representing, directly or by implication, that, such product is effective, or therapeutically superior to any other drug, for any disease, symptom or condi-

tion, unless at the time such representation is made respondent possesses and relies upon a reasonable basis for such representation, which shall consist of competent and reliable scientific evidence. In the case of comparative representations regarding a nonprescription internal analgesic drug product, other than representations of pharmaceutical quality, "competent and reliable scientific evidence" shall be defined as the evidence described in Part II(E) of this Order. In case of representations of pharmaceutical quality, the provisions of Part III of this Order shall apply. For the purposes of this Order, "a representation concerning the pharmaceutical quality" shall mean any representation concerning the manufacturing processes or pharmaceutical quality (such as quality, purity, stability or product formulation) of a [346] nonprescription internal analgesic product which does not refer, directly or by implication, to the speed, onset, duration or intensity of action or to adverse effects.

II.

It is further ordered, That respondent Sterling Drug, Inc., a corporation, its successors and assigns and respondent's officers, agents, representatives and employees directly or through any corporation, subsidiary, division or other device, in connection with the labeling, advertising, offering for sale, sale or distribution of any nonprescription drug in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from:

A. Representing that such product contains any ingredient, or combination of ingredients which is unusual, special or exclusive when such ingredient, or combination of ingredients, is available in other nonprescription analgesic products.

B. Referring, directly or by implication, to aspirin, caffeine or any commonly known ingredient by any word or words without disclosing the common, or usual, name of such ingredient. [347]

C. Failing to disclose in the advertising of such nonprescription drug product the presence of aspirin when such product contains such ingredient.

D. Misrepresenting, in any manner, any test, study or survey or any or all of the results thereof.

E. Representing, directly or by implication, that a claim concerning the comparative effectiveness or comparative freedom from side effects of any internal analgesic product has been established unless such representation has been established by two or more adequate and well-controlled clinical investigations, conducted by experts qualified by training and experience to evaluate the effectiveness and

comparative effectiveness or comparative freedom from side effects of the drugs involved, on the basis of which it could fairly and responsibly be concluded by such experts (1) that the drug will have the **[348]** comparative effectiveness or comparative freedom from side effects it is represented to have, and (2) that such comparative effectiveness or comparative freedom from side effects is demonstrated by methods of statistical analysis, and with levels of confidence, that are generally recognized by such experts. At least one of the adequate and well-controlled clinical investigations to evaluate the comparative effectiveness of the drug shall be conducted on any disease or condition referred to, directly or by implication; or, if no specific disease or condition is referred to, then the adequate and well-controlled clinical investigations shall be conducted on at least two conditions or diseases for which the drug is effective. To provide the basis for the determination whether any clinical investigation is "adequate and well-controlled," the plan or protocol for the investigation and the report of the results must include the following:

1. A clear statement of the objective of the investigation. **[349]**
2. A method of selection of the subjects that:

a. Provides adequate assurance that they are suitable for the purposes of the investigation, and diagnostic criteria of the condition to be treated (if any);

b. Assigns the subjects to the test groups in such a way as to minimize bias;

c. Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease or condition (if any), and use of drugs other than the test drugs.

3. An explanation of the methods of observation and recording of results, **[350]** including the variables measured, quantitation, assessment of any subject's response, and steps taken to minimize bias on the part of the subject and observer.

4. A comparison of the results of treatments or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. The investigation must be conducted double-blind, and methods of double-blinding must be documented. In addition, the investigation must contain a placebo control to permit comparison of the results of use of the test drugs with an inactive preparation designed to resemble the test drugs as far as possible.

5. A summary of the methods of analysis and an evaluation of data derived **[351]** from the study, including any appropriate statistical methods.

F. Making any representation, directly or by implication, concerning the comparative effectiveness or comparative freedom from side effects of any internal analgesic product, when there exists a substantial question, recognized by experts qualified by scientific training and experience to evaluate the efficacy and safety of such drug product, as to the validity of any such representation, unless respondent discloses the existence of such substantial question by including in the same advertisement a clear and conspicuous disclosure statement conforming to the following:

1. The disclosure statement regarding Bayer Aspirin shall state "Bayer Aspirin has not been proven to be therapeutically superior to other plain aspirins," or comprise such other statement approved by the Federal Trade Commission in advance or as respondent can demonstrate [**352**] (based on consumer surveys whose design is adequate and previously approved by the Federal Trade Commission) will convey the same message to consumers.

2. The disclosure statement regarding Bayer Children's Aspirin shall state "Bayer Children's Aspirin has not been proven to be therapeutically superior to other children's aspirins," or comprise such other statement determined and approved as set forth in 1 hereinabove.

3. The disclosure statement regarding Vanquish or Cope shall state "Vanquish [or Cope] has not been proven to be more effective [or faster or gentler] than aspirin," or comprise such other statement determined and approved as set forth in 1 hereinabove.

4. In print advertisements, the disclosure shall be displayed in type size which is at least the same size as that in which the principal portion of the text of the advertisement appears and shall be separated from the text so that it can be readily noticed. [**353**]

5. In television advertisements, the disclosure shall be presented simultaneously in both the audio and video portions. During the audio portion of the disclosure in television and radio advertisements, no other sounds, including music, shall occur. Each such disclosure shall be presented in the language principally employed in the advertisement.

III.

It is further ordered, That respondent Sterling Drug, Inc., a corporation, its successors and assigns and respondent's officers, agents, representatives and employees directly or through any corporation, subsidiary, division or other device, in connection with the labeling, advertising, offering for sale, sale or distribution of any nonprescrip-

tion drug in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from making any representation, directly or by implication, concerning the pharmaceutical quality of any nonprescription drug product manufactured or distributed by it, unless at the time such representation is made respondent possesses and relies upon a reasonable basis for such representation, which shall consist of competent and reliable scientific evidence. In the case of [**354**] such comparative representations, "competent and reliable scientific evidence" shall mean a pharmaceutical or physicochemical study or survey designed and conducted according to sound scientific procedures, by experts qualified by training and experience to evaluate the pharmaceutical quality or comparative pharmaceutical quality of the drug product class, on the basis of which it could be fairly and responsibly be concluded by such experts (1) that the drug product has the comparative pharmaceutical quality it is represented to have, (2) that such comparative pharmaceutical quality, to the extent suceptible of quantitation, is demonstrated by methods of statistical analysis, and with levels of confidence, that are generally recognized by such experts, and (3) that such comparative pharmaceutical quality has clinical significance. Such scientific procedure shall also include (4) appropriate controls of test samples for their age and condition of storage in a way generally accepted by such experts and (5) the nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the results. The study must be conducted double-blind to the extent appropriate.

IV.

It is further ordered, That respondent Lois Holland Callaway, Inc., a corporation, its successors and assigns, and [**355**] respondent's officers, agents, representatives and employees directly or through any corporation, subsidiary, division or other device, in connection with the labeling, advertising, offering for sale, sale or distribution of Vanquish or any other nonprescription internal analgesic product in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from:

A. Referring, directly or by implication, to aspirin, caffeine or any commonly known ingredient by any word or words without disclosing the common, or usual, name of such ingredient, or

B. Failing to disclose in the advertising of such nonprescription drug product the presence of aspirin when such product contains such ingredient.

So much of Complaint Paragraph Twenty-Nine as it relates to Complaint Paragraph Seventeen is hereby dismissed.

OPINION OF THE COMMISSION

BY CLANTON, *Commissioner.*

I. INTRODUCTION

The American Indians knew that you could make a medicine for treating pain from the leaves and bark of the willow tree. However, it was not until the mid–1800's that acetylsalicylic acid (a substance similar to the salicin contained in willows) was synthesized and at the end of the 19th century it was first marketed commercially under the trade name "Aspirin" by the German concern, Farbenfabriken Bayer AG. During World War I the United States government seized Bayer's American assets and these (including the "Bayer" name) were sold in 1918 to Sterling Drug, Inc. ("Sterling"). At about the same time, the patent on the manufacturing process expired and shortly thereafter Sterling lost the "Aspirin" trademark in private litigation.[1] [2]

Nonetheless, for many years, Bayer aspirin ("Bayer") remained the nation's leading over-the-counter ("OTC" or nonprescription) analgesic (pain reliever). In recent years, competition from other aspirin and acetaminophen-based analgesics has eroded Bayer's market share to the point that it is no longer the market leader. In order to stave off this decline, Sterling has devoted a substantial amount of money to advertisements for its aspirin. In fact, from 1967 through 1973, Sterling spent $118.5 million on television advertising for Bayer.

In 1973 the Commission issued a complaint against Sterling (and its two advertising agencies, Dancer-Fitzgerald-Sample, Inc., and Lois Holland Callaway, Inc.) charging that advertising for Bayer and for four other analgesic products manufactured by Sterling (Bayer Children's Aspirin, Cope, Vanquish, and Midol) violated Sections 5 and 12 of the Federal Trade Commission Act (15 U.S.C. 45, 52).[2] Specifically, the complaint charged that respondents made the following false, deceptive, or unfair claims:

1) Bayer is therapeutically and qualitatively superior to any other aspirin and this superiority has been shown by tests (Comp. ¶¶ 10(A), 20), and the therapeutic superiority has been established (Comp. ¶ 8(A)(1);

2) Bayer Children's Aspirin is therapeutically superior to any other

[1] *Bayer Co. v. United Drug Co.*, 272 F. 505 (S.D. N.Y. 1921).

[2] On the same date, the Commission issued a complaint against American Home Products regarding its advertising of Anacin and Arthritis Pain Formula and a complaint against Bristol-Myers Company regarding its advertising for Bufferin, Excedrin, and Excedrin P.M.

children's aspirin (Comp. ¶ 10(B)), and this superiority has been established (Comp. ¶ 8(A)(2));

3) Vanquish is a more effective pain reliever than aspirin, buffered aspirin, or the largest selling extra strength tablet (Comp. ¶ 12(B)(1),(C)), and this superiority has been established (Comp. ¶¶ 8(B)(1), (C);[3] [3]

4) Cope is more effective for the relief of "nervous tension headache" than any other OTC internal analgesic (Comp. ¶ 12(A)), this superiority has been shown by tests (Comp. ¶ 18), and this superiority has been established (Comp. ¶ 8(A)(3));

5) Vanquish will result in less stomach upset than any other unbuffered OTC analgesic (Comp. 12(B)(2)), and this superior freedom from side effects has been established (Comp. ¶ 8(B)(2));

6) Bayer, Cope, and Midol can relieve nervous tension (Comp. ¶ 15);

7) Cope is the only OTC analgesic containing both a pain reliever and a sedative (Comp. ¶ 22);

8) The analgesic in Midol is other than ordinary aspirin and its stimulant is other than caffeine (Comp. ¶ 26).

The complaint also alleged that respondent's ads failed to disclose that Vanquish, Cope, and Midol contain aspirin and caffeine (Comp. ¶¶ 23, 24, 25) and that ads for Bayer, Vanquish, and Cope made mutually inconsistent claims regarding the superior effectiveness of Bayer and Cope for the relief of "nervous tension headache," and the freedom from side effects of Bayer and Vanquish (Comp. ¶ 17).

Dancer-Fitzgerald-Sample, Inc. was charged with responsibility for all ads relating to Bayer, Bayer Children's Aspirin, and Cope. Lois Holland Callaway, Inc. was charged with responsibility for some of the ads relating to Vanquish.

This case was assigned to Administrative Law Judge Montgomery K. Hyun,[4] who reached an initial decision on January 30, 1981, finding against Sterling on all charges except for the charge related to the making of inconsistent claims. The advertising agency, Dancer-Sample-Fitzgerald, Inc., was dismissed by Sterling in 1976 and entered into a consent order settling the charges against it. 96 F.T.C. 1 (1980). Lois Holland Callaway, Inc. became insolvent and its creditors' committee chose not to defend in this suit. The ALJ found that the ad agency had adequate substantiation for the comparative efficacy and

[3] Complaint paragraph 8(C) does not specifically allege that respondents represented that Vanquish's superior efficacy over the leading "extra-strength" tablet has been established. However, since it appears that it was complaint counsel's intent to allege establishment, and since it appears to have been the parties' understanding that establishment had been alleged (*see* Contested Issues of Fact ¶¶ 2(d), 2(e), 2(f)) and since the issue was tried by the parties (*see* p. 89 of the Initial Decision), we will treat this issue as though it had been appropriately pleaded (*see* F.T.C. Rules of Practice Section 3.15(2), 16 C.F.R. 3.15(2)).

[4] The companion cases against American Home Products Corp. and Bristol-Myers Company were also heard by Judge Hyun.

safety claims it made regarding Vanquish, but he found it liable for failing to disclose the presence of aspirin in Vanquish. [4]

This matter is now before us on the appeal of both respondent Sterling and complaint counsel. Sterling's principal contentions on appeal are:

1) the ALJ erred in finding that Sterling's ads made representations of therapeutic superiority;

2) the ALJ applied inappropriate substantiation standards to the ads;

3) contrary to the ALJ's decision, the nonclinical evidence in the record provides a reasonable basis for the conclusion that Bayer is pharmaceutically and therapeutically superior to other aspirin;

4) the ALJ erred by excluding scientific materials proffered by Sterling; and

5) the order entered by the ALJ is overbroad.

Complaint counsel support the ALJ's order but argue that it should be broader. Specifically, they argue:

1) the order should require the same amount of substantiation for superior quality claims as for therapeutic superiority claims;

2) the order should have broader product coverage;

3) the order should define the substantiation necessary for noncomparative tension claims;

4) corrective advertising should have been required;[5] and

5) Sterling should have been prohibited from making mutually inconsistent performance claims for its products.

Although many of the issues in this case are similar to those recently considered by the Commission in *American Home Products,* 98 F.T.C. 136 (1981), *aff'd,* 695 F.2d 681 (3rd Cir. 1982), and *Bristol-Myers,* Docket No. 8917 (1983) [102 F.T.C. 21], there are some notable differences. As the Commission noted in *American Home Products,* 98 F.T.C. at 362, because aspirin is so homey and commonplace, "a maker of one aspirin-based pain reliever seeking [5] to differentiate its product from the rest faces a formidable marketing task." In order to accomplish this task, both American Home Products and Bristol-Myers attempted to dissociate their products from aspirin and then represent them as special and more effective. Sterling took a different approach. The advertising for Sterling's principal product, Bayer, specifically emphasizes the aspirin content of that product and its superiority over other aspirin-based analgesics. Rather than trying to

[5] Although complaint counsel indicated they did not intend to press the corrective advertising issue (Transcript of Oral Argument p. 27), they did brief this issue and we have dealt with it in this opinion (*infra* pp. 60–61).

disguise the aspirin ingredient,[6] respondent's ads trumpet the fact that Bayer contains aspirin and that, based on tests of competing products, Bayer is the best aspirin on the market. Sterling emphasizes that its advertising for Bayer benefitted the public because it was the only defender of aspirin. It argues that its ads countered "the tremendous volume of advertising" for combination products which "disparag[ed] aspirin." (Transcript of Oral Argument p. 13) Among these "disparaging" ads placed by Bayer's competitors are ads challenged in *American Home Products* and *Bristol-Myers*. Sterling further contends that its advertising was designed to show that the combination products all contained aspirin and that Bayer was as effective as any of them.

The Commission, of course, does not dispute the value of providing consumers with specific product information, especially information which facilitates product comparison. In fact, we encourage that kind of advertising.[7] The issue here, however, is whether Sterling's advertising made certain claims and whether those claims were supportable. In particular, a principal, and unique, focus of this proceeding concerns the extent to which general therapeutic superiority claims can be inferred from representations expressly referring to particular product attributes such as purity, freshness and speed of disintegration. Respondent argues that these ads make only manufacturing quality claims and that manufacturing quality is distinct from therapeutic superiority.[8] As we discuss more fully below, we believe that some of respondent's ads do make therapeutic superiority claims and references to scientific tests in those ads imply that the superiority of Bayer (and Cope) has been established.[9]

In connection with these claims of established therapeutic superiority, we find no reason to depart from our conclusions in *Bristol-Myers* and *American Home Products* that these claims must be supported by well-controlled clinical studies, evidence which Sterling lacked in this case. We also find that some of the separate product attribute claims (or pharmaceutical quality [6] claims) made by Sterling were misleading in light of the evidence relied upon to support those representations. Finally, our decision addresses a variety of other charges concerning noncomparative tension relief claims, unusual ingredient claims and material omission claims that are similar to issues considered in our other analgesic cases. We do note, at this point, two additional differences between this case and those

[6] While there are allegations of failure to disclose aspirin content for Midol, etc., those issues are secondary here to the principal claims involving Bayer.

[7] Indeed, we find ads such as CX 31 unobjectionable.

[8] For a discussion of the difference between manufacturing quality and therapeutic superiority, *see infra* pp. 11–12.

[9] The meaning of "establishment" claims is discussed in *American Home Products*, 98 F.T.C. at 373–376 and in *Bristol-Myers*, slip op. at 18–19 [102 F.T.C. at 331–332].

involving Sterling's competitors, Bristol-Myers and American Home Products. Unlike those cases, the complaint in this matter includes allegations that respondent's therapeutic superiority claims lacked a reasonable basis. Another allegation, unique to this case, is that some of respondent's advertising claims were mutually inconsistent. Complaint counsel contend this practice should constitute a separate violation of the Section 5 of the F.T.C. Act.[10]

II. COMPARATIVE EFFICACY AND SIDE EFFECTS CLAIMS

A. *The Advertisements.*

Paragraphs 8–14 and 18–21 of the complaint allege that respondent Sterling made comparative performance and freedom from side effects claims for Bayer, Bayer Children's Aspirin, Vanquish, and Cope and that these claims were not properly substantiated. In discussing these allegations, we first review respondent's advertisements. It is well settled that the Commission can interpret the meaning of advertisements without necessarily referring to extrinsic evidence. *Bristol-Myers,* slip op. at 4 [102 F.T.C. at 319], *The Kroger Company,* 98 F.T.C. 639, 728 (1981). However, when extrinsic evidence is presented to assist in interpreting ads, that evidence must be considered. *Cinderella Career and Finishing Schools, Inc.* v. *F.T.C.,* 425 F.2d 583, 588 (D.C. Cir. 1970). Accordingly, we have examined all the evidence which has been presented including the ads themselves, expert testimony and copy test results. Additionally, when interpreting advertisements, we consider the net impression made by the ad. *American Home Products* v. *F.T.C.,* 695 F.2d at 687; *Beneficial Corp.* v. *F.T.C.,* 542 F.2d [7] 611, 617 (3rd Cir. 1976), *cert. denied,* 430 U.S. 983 (1977). Therefore, we analyze each challenged advertisement as a whole.[11]

Sterling argues that its ads must also be examined in light of the advertising of its competitors to which it was attempting to respond. (R.A.B. p. 5) Although such a comparison may be helpful in interpret-

[10] The following abbreviations are used in this opinion:

F.	–	Initial Decision, Finding No.
I.D.	–	Initial Decision
CX	–	Complaint Counsel's Exhibit No.
RX	–	Respondents' Exhibit No.
Tr.	–	Transcript of Testimony, Page No.
C.A.B.	–	Complaint Counsel's Appeal Brief
C.An.B.	–	Complaint Counsel's Answering Brief
R.A.B.	–	Sterling's Appeal Brief
R.An.B.	–	Sterling's Answering Brief

[11] In interpreting ads, the Commission is concerned not only with representations conveyed by literal statements, but also with representations reasonably implied by the ads. However, we may not inject novel meanings into ads and then condemn them as unsupported. If an ad conveys more than one reasonable meaning and any one of these meanings is false, that ad may be found in violation of the law. Bristol-Myers, slip op. at 4–5 [102 F.T.C. at 319–320].

Challenged claims must also be material, *i.e.,* likely to influence consumers' purchasing decisions. In this case respondent has not raised any argument regarding materiality. False superiority claims are material because they may discourage consumers from shopping for less expensive and potentially equally effective alternatives. (*See* F. 11) Unsubstantiated tension-relief claims are material because they may encourage excessive use of aspirin, a potentially harmful drug, or otherwise discourage consumers from purchasing more effective products.

ing advertising, it cannot excuse the failure to adequately substantiate the claims which are clearly made in Sterling's ads. Sterling is accountable for the advertising which it promulgated, *see Chrysler Corp.*, 87 F.T.C. 719, 752 n. 43 (1976), and it cannot justify its failings by pointing to the conduct of its competitors. (Indeed, we have already found two of its major competitors in violation of the law.)

The complaint against Sterling alleges that it made eight comparative superiority claims for Bayer, Bayer Children's Aspirin, Vanquish and Cope. The ALJ found that Sterling's ads made all eight of the claims. In addition, the complaint alleges Sterling represented that seven of these claims had been established and the ALJ also found all seven establishment representations had been made. We agree with the ALJ that Sterling's ads make some of the alleged representations and we further agree that three of the comparative claims are represented as having been established. However, we find that some of the ads cited by the ALJ as making certain representations do not make those representations. Further, as we indicated above, we disagree with the ALJ's conclusion that every ad which makes a comparative superiority claim represents that the superiority has been established.

As we described in *Bristol-Myers*, slip op. at 6 [102 F.T.C. at 321], the complaints in these cases require us to distinguish three distinct types of comparative efficacy and freedom from side effects claims. The first group consists of "establishment claims," or claims that superiority has been scientifically *established.* This kind of representation may be made through the use of specific language, such as "medically proven" or through the use of visual aids, such as scientific charts and white-coated technicians. *See American Home Products,* 98 F.T.C. at 374–375. The second type consists of claims of superiority without any indication superiority has been established. An advertiser must [8] possess a reasonable basis for making this type of claim. *See Pfizer, Inc.*, 81 F.T.C. 23 (1972) The third type of claim is puffing, for which no substantiation is required. Puffing claims are usually either vague or highly subjective and, therefore, incapable of being substantiated.[12] Each of respondent's claims can be placed in one of these three groups and the substantiation necessary is dependent upon that characterization.

1. Claim that Bayer is therapeutically superior to any other aspirin.[13]

Paragraph 10(A) of the complaint alleges that Sterling represented

[12] The claim "Bayer works wonders" in CX 27 is an example of puffing.

[13] Complaint paragraphs 8(A)(1) and 10(A).

in its advertisements that Bayer is therapeutically superior to any other aspirin. The ALJ found that Sterling's ads made this claim. We agree with respect to some of the advertisements, but disagree with respect to others.

In evaluating Sterling's advertisements, it is important to understand the relationship between therapeutic effectiveness and "manufacturing quality" (also referred to as "pharmaceutical quality" or "product quality"). Therapeutic effectiveness refers to the medical effects of a drug—its effectiveness as a pain reliever, its freedom from unwanted side effects, and so on. By contrast, manufacturing or pharmaceutical quality refers to the care with which a product containing the drug was manufactured—*e.g.,* its purity (freedom from contaminants), any tendency of the pills to crumble or deteriorate over time, or the ease with which the pills can be dissolved. A recurring issue in this case is whether Sterling's ads made claims of superior therapeutic effectiveness, or whether they claimed only superior manufacturing quality.

We agree with the ALJ that Sterling made representations of therapuetic superiority in some instances. For example, CX 161 states:

> . . . Bayer tested its aspirin for quality against the other leading brands . . . 220 brands in all. 30 separate tests were conducted in 14 different categories. . . . During the 4-year study, tests [9] were made for purity, freshness, speed of disintegration, aspirin content, tablet count, overall quality control.
>
> The results were clear. Bayer was consistently superior. . . .

For several reasons we believe this ad represents that Bayer is therapeutically superior. First, the ad implies Bayer disintegrates faster than the other tested aspirins. As we discussed in *Bristol-Myers,* slip op. at 7 [102 F.T.C. at 322], consumers could reasonably infer that an aspirin that disintegrates faster provides relief faster. Since consumers want relief from pain as rapidly as possible, a pain reliever that works faster would reasonably be considered by consumers to be more effective.

Second, the reference to speed of relief is supplemented by the comprehensive nature of the comparative study. The ad emphasizes that 30 separate product attributes were tested. Although only six of those attributes are specifically mentioned, consumers could reasonably assume that some of those tests related to product effectiveness not only because of the reference to speed of disintegration but also because of the clear statement that a wide variety of attributes was

tested. After all, in purchasing aspirin, consumers are primarily concerned that the product purchased be able to relieve pain.

Respondent argues that this ad and others like it (*e.g.*, CX 47, 48, 79, 109, 155–158) actually discuss manufacturing quality and that speed of disintegration is just another attribute of manufacturing quality. It is true that these ads do mention specific product attributes (such as shelf life) that are not necessarily synonymous with a product's comparative therapeutic efficacy. Nevertheless, the ads refer to product characteristics, such as speed of disintegration, that are closely related to efficacy. In addition, the ads speak in such sweeping terms about quality that a consumer could reasonably infer that the tests measured Bayer in all respects, including efficacy. Certainly nothing in the ad indicates that the tests were limited to attributes relating to manufacturing quality. It is hardly reasonable to expect consumers to guess, without any prompting, that Bayer's tests of aspirin "for quality" omitted the very attribute (efficacy) that consumers value the most.

Respondent also argues that testimony of its expert witness, Dr. Miles, indicates that these ads only make representations regarding quality. (R.A.B. p. 8) We have examined Dr. Miles' testimony and find that although she said she reviewed all of the [**10**] challenged ads (Tr. 9258), she only discussed one of the ads listed above, CX 157. (Tr. 9331–33) Dr. Miles did state that she believed the ad made an "unambiguous quality representation." (Tr. 9332) Nevertheless, it was her opinion that consumers reading (or viewing) an ad such as this one would not infer a message of superior efficacy because consumers do not devote much mental effort to ads: "As I said before, they don't make inferential leaps. They don't do a lot of processing of advertising claims. They don't rationally process advertising communication." (Miles, Tr. 9311, 9333)[14] However, we believe that this analysis actually leads in the opposite direction. Efficacy is the most important feature of an analgesic, and a test of numerous product attributes designed to measure product "quality" would normally be assumed to test efficacy. Only upon application of substantial mental effort (effort which Dr. Miles believed the viewer was unlikely to apply) would it occur to a consumer that none of the tests mentioned in the ad directly measured therapeutic efficacy, and that perhaps effectiveness was *not* tested. Thus, we find that these ads[15] do represent that Bayer is therapeutically superior to other aspirin.

The ALJ also found that a representation of therapeutic superiority was made by advertisements claiming that Bayer was the best pain

[14] Dr. Miles indicated that consumers did not devote mental effort to the Bayer ads because they were boring, poorly made, dull, and not memorable. (Tr. 9259, 9273, 9295, 9303, 9304, 9309)

[15] CX 47, 48, 79, 109, 155–158, 161.

reliever or the best aspirin. (F. 294(b)) Once again, we agree that the representation was made at least by some of the ads cited in the ALJ's decision, although we place less reliance than did the ALJ on the ads' closing tag line. For example, CX 52 is a television ad featuring golfer Lee Trevino. He first describes an AMA study which indicates that aspirin is preferred *over combination products* for relief of pain (*i.e.*, on grounds of therapeutic efficacy). After referring to a separate study on aspirin performed by Bayer, he states, "You see, Bayer tested its aspirin for quality, for purity and for freshness against 220 other brands. The tests showed that Bayer makes the superior aspirin." The ad closes with the tag line, "Aspirin is the best pain reliever. And Bayer is the best aspirin." Because of the emphasis in the ad on the AMA report and the comparative aspirin study, consumers could naturally assume that the comprehensive comparative testing performed by Sterling included tests of relative effectiveness. This inference is especially likely given the fact that Sterling's test is mentioned in the context of the AMA report, which implies that aspirin is more effective than other pain relievers. The tag line at the end of the ad does nothing to alter the impression of therapeutic superiority created by the entire ad.

Respondent argues that the "Bayer is the best aspirin" portion of the tag line is puffing which consumers would not take seriously. To support this, it cites Dr. Miles (RAB p. 9–12). However, what Dr. Miles says is that the phrase [11] "world's best aspirin" is puffery and the phrase, "best [aspirin], all by itself is not likely to lose its puffery characteristic and take on some kind of superior therapeutic meaning." (Miles, Tr. 9271) We agree with this. Indeed, we find that in ads such as CX 13 the phrases, "Bayer is 100% aspirin—the world's best aspirin," and "Bayer works wonders," are merely puffing because the ad does not discuss any comparison of Bayer's "quality" with other brands of aspirin.[16] CX 52 is different. That ad mentions the AMA report and the Sterling test comparing 220 brands of aspirin. The tag line does not appear "all by itself," but appears in a context which invites the viewer to conclude that Bayer is therapeutically superior to other aspirin.[17]

Respondent also argues that the two parts of the tag line should be analyzed separately. It argues that the "Bayer is the best aspirin" portion of the tag line should be considered only in light of the study comparing Bayer to other aspirin. Although respondent would apparently agree that the AMA study involved comparative efficacy, it argues that the Bayer study concerned pharmaceutical or manufac-

[16] *See also*, CX 15, 19, 37, 38, 39, 117, 122, 123, 126, 145, 146, 147, 150, 152.

[17] Other similar ads which imply therapeutic superiority and contain the tag line are CX 50, 54, 56–64, 67–70.

turing quality only and that, therefore, the "Bayer is the best aspirin" tag line implies only pharmaceutical superiority.

We recognize (along with the ALJ, F. 322) that pharmaceutical or manufacturing quality is an attribute of analgesics which may, in some circumstances, be distinct from therapeutic quality. But since consumers buy aspirin only to reduce fever, alleviate pain or lessen inflammation, quality, the ability of a product to do what it is supposed to do, is closely linked to efficacy. In ads such as CX 52 and others which mention Sterling's test of 220 brands of aspirin, no effort has been made to limit the claim to non-therapeutic quality characteristics.[18] Each of these ads implies that Sterling's comparative testing was comprehensive by virtue of both the number of brands and variety of attributes tested. As we mentioned before, the natural inference is that efficacy, the most important feature of any analgesic, was also tested. Although these ads do speak of "quality," that term has not been limited to non-therapeutic quality. Thus, we do not agree with respondent that the mention of Bayer's superiority in the 220 test refers only to quality attributes distinct from efficacy. [12]

However, we do not mean by our decision to prevent Sterling from conveying information regarding Bayer's pharmaceutical or manufacturing quality. Indeed, we recognize that this information may be valuable to consumers. And, even though pharmaceutical quality is closely linked to therapeutic quality, it is certainly possible to convey information limited to non-therapeutic quality attributes. For example, CX 72 states in part, "Sometimes you can even smell a difference in aspirin. If you sense a vinegary odor, that's a sign of possible deterioration. So to get the best quality aspirin, always get Bayer." This ad discusses a particular attribute of product quality, shelf life, that consumers would understand as distinct from therapeutic superiority.[19] Although representations of superior "quality" will usually imply therapeutic superiority, that is not so with respect to CX 72 because it carefully defines product quality in terms of shelf life and thereby avoids making any representation regarding therapeutic superiority.

Respondent finally argues that it was improper for the ALJ to rely upon copy test results (F. 300–302) because the Zeisel Study (CX 520) to which he referred was flawed and because it showed that only a small percentage of consumers (11% for one ad and 13% for another) received a superior efficacy message from two of the ads (CX 52, 157) in question. (RAB p. 13 n. 20) The ALJ did, in fact, find that the Zeisel Study was flawed and that the questions asked of test participants

[18] Other similar ads which imply therapeutic superiority are CX 73–78, 80–83, 105–108, 110–116, 162, 163.

[19] A product with a longer shelf life may well be no more efficacious than one with a shorter shelf life. However, it will maintain its quality for a longer time.

were leading. For this reason, he rejected the results of all but the first two questions asked of participants. (F. 201) Furthermore, the only two questions which the ALJ found unobjectionable direct participants to the ad's major point. For this reason, it appears unlikely that the study would capture inferences and additional meanings drawn by consumers from the ad. Thus, the Zeisel Study cannot confirm respondent's interpretation of the ads. Indeed, another copy test in the record, CX 568 (performed by Audience Studies, Inc.), evaluated CX 50, an ad similar to CX 52. It showed that more than 22% of test participants drew a message of superior efficacy from the ad. On balance, the copy test evidence is not especially helpful because the Zeisel Study was flawed and because its results were contradicted by CX 568. However, in this instance, the representation of Bayer's therapeutic superiority flows clearly and logically from the ads. Therefore, copy tests were not necessary to aid in our interpretations.

2. Claims that Bayer's therapeutically superiority to any other aspirin is established.

Paragraph 8(A) of the complaint charges Sterling with having represented that the truth of the therapeutic superiority claims for Bayer had been established. The ALJ concluded that every [13] ad which made a representation of superior therapeutic efficacy also made an establishment claim, because consumers believe scientific evidence supports every claim of superiority regarding drugs. While we reject the ALJ's reasoning, we reach the same conclusion regarding the advertisements at issue in this case.

Respondent argues there is no justification for the ALJ's conclusion that any ad which makes a therapeutic superiority claim necessarily represents the claim is scientifically established. Sterling notes that a substantial number of ads cited by the ALJ do not mention tests at all, and those ads which do mention tests of Bayer indicate that only quality attributes were tested. (RAB pp. 14–17)

In *Bristol-Myers,* the record did not contain sufficient evidence to sustain the argument that consumers believed that every claim of superiority for an analgesic drug has been established to the satisfaction of the scientific community. Slip op. at 40–41 [102 F.T.C. at 350–351]. For the same reason—since no additional evidence has been presented in this case—we reach the same conclusion here. Nevertheless, as we also stated in *Bristol-Myers,* consumers *would* reasonably infer that a proposition in an ad has been scientifically established if the ad uses language or visual aids which suggest such a foundation. *Id.* at 6 [102 F.T.C. at 321]. Indeed, in this case all of the challenged ads in which we find a representation that Bayer is therapeutically superior include language and pictures which suggest Bayer's thera-

peutic superiority has been proven. All of the ads rely heavily on the AMA report and/or Bayer's own tests.

In *Pfizer,* the Commission found that the challenged ads portrayed a frivolous aura and thus, even though the ads mentioned tests, they did not convey serious scientific overtones. 81 F.T.C. at 59. Here, the opposite is true. Not only are the challenged ads serious in tone but also the format of the ads listed above generally consists of objective evaluations (based on tests) of Bayer's superiority, thus contributing to the scientific aura of these ads. In the ads which mention speed of disintegration, the impression that tests support Bayer's superiority is enhanced by a picture of the AMA report (*e.g.,* CX 155, 156) or by a picture of a booklet containing the results of Sterling's aspirin comparison tests (*e.g.,* CX 47, 48, 157, 158, 161). Even in those instances in which the ads do not mention speed of disintegration, the ads do indicate that Sterling's testing was comprehensive, in terms of both the number of brands included and the number of attributes tested. As discussed above (*supra* pp. 11–12), the natural inference is that these tests measured efficacy and demonstrated Bayer's superiority.[20] [14]

3. Claim that Bayer has been tested and found pharmaceutically and therapeutically superior to all other aspirin tested.

Paragraph 20 of the complaint alleges that respondent's ads represent that Bayer has been tested against 220 other brands of aspirin for quality, purity, freshness, stability, and speed of disintegration and that the tests demonstrate that Bayer is superior to the other brands in all these categories. The ALJ found that advertising for Bayer represented it was superior in overall quality and superior with respect to each of the other four listed attributes. We agree.

Numerous ads discuss the results of tests comparing Bayer with other aspirin. All of those ads indicate that Bayer was compared for quality against other aspirin.[21] The clear message is that the tests showed Bayer to be superior. For example, CX 108 states, "Bayer tested its aspirin for quality against all major brands of aspirin. And Bayer came out way ahead for quality." Other ads use such language as: "For quality—Bayer was shown superior" (CX 76), "The aspirin that tested better for quality" (CX 74), "Bayer was consistently better" (CX 109). In addition, some of the ads that mention the comparison mention specific attributes that were tested: purity (*e.g.,* CX 61,

[20] We do not mean to suggest that every reference in an ad to a study or test necessarily implies that the underlying claim has been scientifically proven or established. (Indeed, *Pfizer* itself is sufficient to disprove this notion.) What we do suggest is that where scientific evidence is cited in support of a claim, absent some explicit qualification it is unlikely that consumers would interpret such evidence narrowly to provide proof for only a limited portion of the claim.

[21] The tests comparing Bayer with other aspirin are mentioned in CX 47, 48, 50, 52, 54, 56–64, 67–70, 72–83, 101–116, 155–158.

79, 109), freshness (CX 47, 73, 155), stability (CX 79, 156, 158), and speed of disintegration (CX 48, 109, 157). Although the ads do not directly state that the tests showed Bayer superior for any specific attribute, superiority with respect to these attributes is clearly implied by the ads. For example, CX 79 states, "Bayer tested its aspirin against every other leading brand. For purity, stability, speed of disintegration, Bayer was consistently better." This ad and others like it (CX 109, 155, 156, 158) focus on the attributes tested as well as overall quality.

Paragraph 20 also charges that the comparative tests demonstrate Bayer's *therapeutic* superiority. This allegation is essentially identical to paragraph 10(A) of the complaint. Since we have previously determined that numerous ads describing Sterling's comparative tests represent Bayer's therapeutic superiority (*supra* pp. 8–12), there is no need to repeat that analysis here. [15]

4. Claims that Bayer Children's Aspirin is therapeutically superior to other children's aspirin and that this superiority has been established.

Paragraph 10(B) of the complaint alleges that respondent represented in its advertising that Bayer Children's Aspirin is superior to other children's aspirin in terms of significant therapeutic effect. Paragraph 8(A)(2) contains the corresponding establishment charge. The ALJ found that both of these representations were made by the challenged advertisements. (F. 339–351) In this instance, we agree with respondent and can find no representation of therapeutic superiority in any of the challenged ads.

For example, CX 183 states:

> It's a fever. But you know what to do. Doctors recommend aspirin to reduce the fever of a cold and relieve the aches. And you choose Bayer Children's Aspirin because when your child is sick, it's good to know you have Bayer behind you. You and Bayer. You take extra care to keep the aspirin safely stored. Bayer takes extra care to keep the aspirin pure and fresh by making over 200 quality control tests on every group of tablets. Part of a special Bayer process. You take extra care to read the label and give the right dosage. Bayer takes extra care by blending two kinds of aspirin crystals instead of one so its aspirin disintegrates smoothly and gently. Part of a special Bayer process. So when your child is sick, its good to know you have Bayer behind you.

For several reasons, this ad does not represent that Bayer is therapeutically superior. First, although the ad does indicate the Bayer manufacturing process is special, the overall impression created by the ad is not one of uniqueness. To be sure one could reasonably infer from this ad that Bayer Children's Aspirin is a good product or even that it is one of the best brands of children's aspirin available. But that

characterization does not constitute a representation that Bayer Children's Aspirin is *the best* children's aspirin. In addition, a central theme of this ad is that Bayer Children's Aspirin is a well-made aspirin. Unlike ads for regular Bayer discussed above (*supra* pp. 8–12) CX 183 does not stress a comparison between Bayer Children's Aspirin and all other brands. Indeed, the tests that are mentioned are quality control tests, not comparative tests. The ad does not in any way imply that Sterling is the only manufacturer which performs such tests. Thus, without [16] additional evidence we are unwilling to conclude that consumers would make the inferential leap from the representations in CX 183 to a representation of therapeutic superiority.[22]

Another Bayer Children's Aspirin ad cited by the ALJ is CX 167. That ad states, in part, "No one makes aspirin like Bayer. No one purifies aspirin like Bayer. No one protects aspirin like Bayer." Unlike CX 183, this ad makes a superiority claim for Bayer Children's Aspirin. Nevertheless, the message is not that Bayer Children's Aspirin is therapeutically superior but that Sterling's manufacturing process is superior. As we indicated above in connection with ads for regular Bayer aspirin, a representation of superior manufacturing quality does not necessarily imply therapeutic superiority. (*supra* pp. 11–12) In ads such as CX 167, Bayer Children's Aspirin's superiority is narrowly defined in terms of specific quality attributes. Thus, there is no representation of therapeutic superiority.[23]

Finally, the ALJ discusses CX 176. That ad opens with a mother concerned about a sick child. She consults a doctor, "she keeps the patient quiet and she gives her children's aspirin. . . . She chooses orange-flavored Bayer Aspirin for children because she knows Bayer makes the best children's aspirin." Although this ad does state that Bayer makes the best children's aspirin, the reference to "best" constitutes puffing. The tone is homey, familiar and secure. In this context, "best" implies only that Bayer Children's Aspirin is a dependable product that a parent can feel secure in giving to a sick child.[24]

5. Claims that Vanquish is a superior pain reliever and that that superiority has been established.

Paragraphs 12(B)(1) and 12(C) of the complaint allege that respondent represented in its advertisements that Vanquish is a superior pain reliever to aspirin, buffered aspirin and the largest selling "extra strength" tablet. Paragraphs 8(B)(1) and 8(C) allege this superiority

[22] Other ads which we find do not claim superiority are CX 182, 184, 209.

[23] Other ads representing pharmaceutical superiority only are CX 175, 185, 188, 196, 197, 205.

[24] Other ads in which "best" constitutes puffing are CX 168–170, 176–181, 194, 195, 198, 201–203.

has been established. The ALJ found Sterling had represented that Vanquish was a superior pain reliever to aspirin, buffered aspirin and to the largest selling "extra strength" tablet. We agree with this finding, although we find that some of the ads cited by the ALJ did not make the challenged representations. We also disagree with the ALJ's finding that the ads make establishment claims. [17]

Vanquish is represented as a superior pain reliever to aspirin in CX 224 and 226. CX 224 states:

> Vanquish is different. It gives you the proven effectiveness of aspirin in this tablet, plus extra medications in these. . . . Vanquish is the only leading pain reliever you can buy that combines the extra strength of three medications with two gentle buffers.

The point of this ad is that Vanquish starts with aspirin and adds extra medication. Consumers could reasonably assume that the purpose of this extra medication is to provide "extra strength"—*i.e.,* extra pain relief. As the court noted in *American Home Products* v. *F.T.C.:*

> Not only credulous purchasers are apt to conflate the idea of more pain reliever with that of more pain relief, but as the Commission explains in its brief, even rational and careful consumers will be apt to place such an interpretation on the advertisements, "If the presence of more pain reliever in a product did not result in greater pain relief (as may well be true of Anacin), disclosure of the extra amount could be a clear liability since consumers would logically expect that it contributed to an increased price." 695 F.2d at 696.

Another ad, CX 226, represents that Vanquish is a superior pain reliever because it has more ingredients than aspirin. In this ad, a man states that he wants more than buffered aspirin for his headache and the announcer notes that Vanquish has added extra medication to buffered aspirin. This clearly implies that Vanquish is a superior pain reliever to aspirin (and to buffered aspirin). CX 245 and 251 also make this implication. Both of these ads state that Vanquish has extra strength which the "leading buffered product" lacks. Ten other ads represent that Vanquish is superior to the largest selling extra-strength tablet.[25] CX 261 is typical of these ads and it states, "Vanquish contains more pain relievers than the largest selling extra-strength tablet."

Respondent argues that Vanquish was introduced in 1966 as a defensive measure to protect Sterling's share of the OTC analgesics market which was being steadily eroded by other "extra-strength" products. It contends that the Vanquish ads were designed not to represent that Vanquish was therapeutically superior but to describe the product to consumers who would [18] otherwise purchase a com-

[25] The ten ads are CX 252, 255, 256, 258–264.

petitor's "extra-strength" product. Although we appreciate that the market for OTC analgesics is highly competitive, it is important that advertisers not compete with false or deceptive advertisements. An advertiser must still be able to substantiate any claims it makes in attempting to compete.

The complaint also alleges, and the ALJ found, that Sterling made establishment claims regarding Vanquish's superiority over aspirin, buffered aspirin, and the largest selling "extra-strength" tablet. He found that the representation of establishment was made by the use of the phrase "medically-proven ingredients" in CX 254 and the phrase, "the proven effectiveness of aspirin" in CX 224. Also, he found that the mortar and pestle used in several of the ads (CX 224, 226) were "chemist's instruments" which help convey the impression that superiority is predicated upon scientific fact.

We are unable to agree that any ad represents Vanquish's superiority has been established. Although the phrase "medically-proven ingredients" might imply scientific testing, the phrase is used only in one ad and that ad does not compare Vanquish with any other product. Similarly, CX 224 states that aspirin has been proven effective but does not indicate or imply that anything has been proven regarding Vanquish. Finally, the mortar and pestle in CX 224 and 226 do not, in the context of those ads, appear to be chemist's instruments. Instead, they are used to demonstrate that Vanquish is a combination of several ingredients. Although in other instances a mortar and pestle might conceivably convey establishment connotations, they do not do so here.

6. Claims that Vanquish will cause less stomach upset than other OTC analgesics and that this representation has been established.

Complaint paragraph 12(B)(2) alleges that respondent represented that because Vanquish contains "gentle buffers"[26] it would cause less stomach upset than any OTC analgesic not containing buffers. Paragraph 8(B)(2) alleges that respondent represented that Vanquish's superior freedom from side effects had been established. The ALJ found respondent had represented Vanquish causes less stomach upset because it is buffered and we agree.

For example, CX 245 discusses the plight of Tuesdee Testa, "a successful female jockey" who "can't afford a headache." The ad observes that "she wants more than just extra strength, she [19] wants gentle action." After several scenes of Ms. Testa in action, the ad comments, "Look—this leading extra-strength pain reliever has no buffers. . . . Vanquish—it gives you extra strength and gentle buffers.

[26] The "gentle buffers" mentioned in the Vanquish advertising are two antacids, aluminum hydroxide and magnesium hydroxide.

Vanquish—all the strength you need for your headache pain, yet gentle enough to your system." This ad implies that Vanquish is gentle because it has buffers and that a product lacking buffers will be less gentle to the system. Respondent argues that it was merely attempting to inform consumers that Vanquish is a multi-ingredient product. However, the ad clearly does more than that. It represents that the buffers in Vanquish make it a product that is less likely to cause stomach upset.[27]

Most of the challenged Vanquish ads promote it as "the only leading pain reliever you can buy that combines the extra-strength of three medications with two gentle buffers," (CX 224) or contain statements such as, "Vanquish is different. It gives you the well-known pain reliever in this tablet, plus extra medication in this tablet and this tablet, and buffers as in this one. Three headache relievers and two gentle buffers. . . ." (CX 241) Statements such as these imply that Vanquish will produce less stomach upset than an unbuffered analgesic. After all, why else would respondent advertise that Vanquish has buffers and some other products do not? Why else would it refer to the buffers as "gentle"? The natural inference from such advertisements is that Vanquish is "gentler" or causes less stomach upset.[28] Indeed, even respondent's expert, Dr. Miles, appears to concede that consumers may draw inferences from the mention of an ingredient in an ad for a product. (Tr. 9492–93.

However, we disagree with the ALJ's finding that the challenged ads represent that Vanquish's superior freedom from side effects has been established. As we stated above consumers would not infer that claims in an advertisement had been established merely because the ad shows a hand using a mortar and pestle to grind tablets. And once again, we disagree with the ALJ's conclusion that every claim of comparative superiority impliedly represents that the superiority has been established. Thus, we find that respondent represented that the presence of buffers in Vanquish causes it to produce less stomach upset than analgesics not containing buffers. However, the ads do not represent that this claim has been established. **[20]**

7. Claims that Cope is more effective than other analgesics and that this representation has been established.

Paragraph 12(A) of the complaint alleges that Sterling's ads represent that Cope is more effective for the relief of nervous tension headache than any other OTC analgesic. Paragraph 8(A)(3) alleges

[27] Other ads disclosing the presence of buffers in Vanquish and containing the statement that Vanquish is gentle to the system are CX 246, 247, 251.

[28] Ads which promote Vanquish as a product containing gentle buffers are CX 224, 226, 235, 236, 241–247, 250–256, 258–264.

that respondent represented that this claim has been established.[29] The ALJ found that all of these claims had been made, and we agree.

CX 272 is typical of the ads for Cope. It states:

> Important studies made at the world's leading headache clinic show that for relief of severe nervous tension headaches a combination of a pain reliever and a sedative provides greater relief than either medication alone. Of all leading remedies you can buy for ordinary nervous tension headaches, only Cope combines a gentle relaxer with a powerful pain reliever for really effective relief.

The clear and direct message of this ad is that Cope is superior for the relief of nervous tension headache to any other analgesic[30] because of the formulation which it alone has. The importance of this formulation is emphasized by the reference to tests in the ad.[31] Respondent again argues that the Cope ads were merely a description of Cope's ingredients designed to introduce the product to the market. (R.A.B. p. 88) However, these ads plainly go further and describe the purpose of Cope's formulation and inform consumers that because of this formulation, Cope gives more effective relief.

This same ad also represents that Cope's superiority has been shown by studies. Read literally, the ad claims studies have demonstrated that a combination of an analgesic and sedative provides greater relief for *severe* nervous tension headache and that Cope with a similar formula provides relief for *ordinary* [21] nervous tension headaches. Given this juxtaposition, it seems reasonable for consumers to infer that if tests show that a combination of sedative and analgesic provides more effective relief for severe nervous tension headache, these results would also support the conclusion that the Cope formula provides more effective relief for ordinary nervous tension headaches. Indeed, this inference is almost inescapable.[32]

There are numerous other indicia of establishment in the ad. It mentions "important studies made at the world's leading headache clinic," the announcer is holding what appears to be a copy of a report, and he is standing in a room lined with ponderous books. The words and the visual images of this ad imply that the basic message of the ad (Cope's superiority) has been established.[33]

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[29] Paragraph 18 alleges that respondent's ads represent that tests or studies prove this superior efficacy. This is the same allegation contained in paragraph 8(A)(3). (*See supra* pp. 14–15)

[30] The Cope ads actually compare Cope to the "leading remedies." Consumers could reasonably assume that a product which is superior to the leading remedies is superior to all remedies.

[31] Other ads which imply that Cope is superior for the relief of nervous tension headache to any other OTC analgesic are CX 273–276, 283, 287, 292–294.

[32] Other ads which imply that Cope's superior efficacy for the relief of nervous tension has been proven by tests or studies are CX 283, 287.

[33] Other ads making an establishment claim are CX 283 and 287.

B. *Required Substantiation for Establishment Claims*

As our analysis of the challenged advertising has shown, Sterling has represented that it is established that Bayer is therapeutically superior to any other aspirin and that it is established that Cope is more effective for the relief of nervous tension headache than any other nonprescription internal analgesic. Paragraph 28 of the complaint alleges that the truth of these claims, in fact, has not been established, and that the establishment claims are, therefore, false. The ALJ agreed. It was his determination that well-controlled clinical studies are necessary to establish an analgesic's comparative superiority, and that Sterling did not possess that sort of evidence.

Sterling has appealed the ALJ's conclusion. First, it argues that the ALJ's approach conflicts with the reasonable basis theory enuciated in *Pfizer* in that *Pfizer* precludes finding a violation based simply on a conflict in scientific opinion. (R.A.B. 20–21) Second, Sterling contends that the establishment (and substantial question) theory has improperly [22] shifted to it the burden of proof. (R.A.B. pp. 21–22) Third, it argues that the ALJ required it to possess substantiation "more extreme than the level of certitude required by Congress and the Food and Drug Administration for the marketing of drugs." (R.A.B. p. 22) Finally, respondent argues that the First Amendment "precludes the proscription or restriction of commercial speech in areas of good faith differences of opinion." (R.A.B. p. 23) We disagree with all of respondent's arguments for the reasons set forth below. We further hold that it did not establish the superiority of either Bayer or Cope.

As we explained in *Bristol-Myers,* the establishment theory is not a new theory of advertising substantiation. Slip op. at 18–19 [102 F.T.C. at 331–332]. It is based on the straightforward notion that when an advertiser represents in its ads that there is a particular level of support for a claim, the absence of that support makes the claim false. Therefore, the inquiry contemplated by *Pfizer* for reasonable basis claims does not conflict with the more narrowly focused inquiry involved where representations are made that a claim has been established or scientifically proven. Indeed, as we noted in *Bristol-Myers* (*Id.* at 18–19 [102 F.T.C. at 331–332]), a similar approach has been used in a number of post-*Pfizer* substantiation cases.

Respondent's argument that the burden of proof has been shifted to it is also incorrect. The complaint alleges that the establishment claims made by Sterling's ads are false. It is complaint counsels' burden to prove the falsity of those claims by proving that the claims have not been established.

Respondent further claims that it is being required to produce an

excessive level of support for its claims. It bases this argument upon the Committee Report accompanying the 1962 amendments to the Food, Drug, and Cosmetics Act which noted that substantial evidence of efficacy is necessary before a drug can be marketed. However, that Report also recognized that there will usually be differences of opinion among scientists regarding the drug. S. Rep. No. 1744, 87th Cong. 2d Sess. part 2 at 6 (1962). We do not prevent respondent from advertising its products when such differences of opinion exist, provided, of course, that it does not represent that the position supporting its products has been scientifically established. To support its establishment claims, we require respondent to have supporting evidence of the type and quantity that is acceptable to the scientific community.

Respondent's constitutional argument also must fail. As respondent has noted in its brief (R.A.B. p. 23), the Supreme Court has indicated that regulation of false, misleading or deceptive advertising is not barred by the First Amendment. *Bates* v. [23] *State Bar of Arizona,* 433 U.S. 350, 383 (1977); *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.,* 425 U.S. 748, 771 (1976). To the extent that respondent claims in its ads that its products' superiority has been established when in fact it has not, the ads are false. There is, therefore, no constitutional impediment to the regulation of respondent's establishment claims.

1. Establishment of Bayer's therapeutic superiority.

A substantial portion of the briefs in this case is devoted to a discussion of the type of evidence necessary to establish the therapeutic superiority of one brand of aspirin over others. Sterling argues at great length that comparative superiority can be demonstrated without the use of well-controlled clinical tests.[34] (R.A.B. pp. 24–42) In support of Bayer's therapeutic superiority, Sterling has presented a substantial amount of nonclinical evidence, including studies comparing impurities in aspirin tablets and evidence regarding the manufacturing of Bayer. Complaint counsel argue that only well-controlled clinical studies can demonstrate the superiority of one brand of aspirin over another. The ALJ agreed with complaint counsel (F. 416) and determined that it has not been established that Bayer is superior to any other aspirin in terms of pain relief and freedom from side effects. (F. 474, 489)

The record contains the testimony of several expert witnesses who testified regarding the type and amount of evidence necessary to

[34] In a well-controlled clinical test, drugs are tested on real patients having actual symptoms. It is not disputed in this case that the elements of a well-controlled clinical test are the use of an appropriate pain model, replication of results, experienced unbiased investigator and adequately trained personnel, a written protocol, double-blinding, use of a placebo control, use of appropriate predetermined analytical techniques, and statistical and clinical significance of the results. (F. 417) *See Bristol-Myers,* slip op. at 24–27 [102 F.T.C. at 335–339].

establish the comparative superiority of one brand of aspirin over others. Based upon our analysis of that testimony, we conclude that at the present time, the relevant scientific community would not regard superiority as established unless supported by the results of well-controlled clinical tests. The record also shows that the only clinical study in the record comparing Bayer with another brand of aspirin (RX 450) does not show any clinically significant difference between Bayer and the other brand tested.

Numerous experts testified for respondent in this case regarding the type of evidence necessary to establish comparative superiority. However, only two of the experts, Drs. Alvan Feinstein [24] and William Fields were qualified as experts in the area of comparative testing of analgesics (F. 110, 115) and the record makes it clear that Dr. Fields had no experience in the testing of mild analgesics (such as the ones involved in this case) (Tr. 16573). Two of Sterling's other experts, Drs. Banker and Rhodes, were qualified only in the formulation and processing of drugs, and neither had any experience with well-controlled tests involving subjective response methodology. (Banker, Tr. 12872; Rhodes, Tr. 11095) Dr. Scoville was qualified only in FDA practices and procedures (F. 134), and he testified regarding the requirements of FDA regulations. The other two doctors who testified on behalf of respondent were Sterling employees who were not qualified as experts in any particular field (Drs. Tainter and Trout; F. 159, 162). Four experts testified for complaint counsel, two of whom, Drs. DeKornfeld and Moertel, were experts in the testing of analgesics (F. 34, 54). The third expert, Dr. Grossman, was qualified as an expert in the field of gastroenterology and aspirin side effects (F. 40) and the fourth expert, Dr. Miller, was qualified as an expert in the formulation and pharmaceutical analysis of drugs. (F. 49).

Although all of these experts have experience with analgesics the record makes it clear that some of them are not experienced in comparing analgesics for the purpose of evaluating relative efficacy. For example, respondent's expert, Dr. Banker, conducted tests of analgesics for the purpose of comparing drug delivery systems[35] (Banker, Tr. 12870), and Dr. Rhodes' tests compared features of drug manufacture such as compaction pressures (Rhodes, Tr. 11084). Neither tested comparative efficacy. Complaint counsel's experts Drs. Grossman and Miller were also not experienced in comparing analgesic efficacy. It is the testimony of experts with experience in the testing of comparative analgesic efficacy that must be given the greatest weight in determining the type of evidence necessary to establish the superiority of one brand of aspirin over others. That testimony (including testimony

[35] A "drug delivery system" is the form given to a dose of a drug. Examples of three delivery systems used for aspirin are tablets, capsules, and effervescent powder.

of respondents' witnesses Drs. Feinstein and Fields) provides strong evidence supporting the conclusion that experts will not regard superiority as established unless that conclusion is supported by clinical evidence.

The need for clinical tests to establish comparative superiority was clearly stated by Dr. DeKornfeld:

> A claim of comparative superiority, I feel quite strongly that a minimum of two carefully controlled clinical comparisons, both showing statistical significance in favor of one of the two compared drugs, is essential to establish the claim of clinical superiority. . . . [M]ost people working [25] in this area will accept two studies showing the same thing done under appropriate circumstances as establishing a claim. If the studies are lacking or if they are controversial, it would not be established. (Tr. 8388, 8391)

Dr. Moertel expressed the same idea. Speaking of clinical testing, he said: "it's the only way we know to properly establish therapeutic superiority. . . ." (Tr. 6255–56) Even respondent's expert Dr. Feinstein indicated that clinical tests provided the best evidence regarding patients' subjective responses. (Feinstein, Tr. 16413)

The experts also explained why clinical tests were necessary. There is general agreement among all the experts that no direct correlation has been demonstrated between the amount of aspirin appearing in the bloodstream at any time and the onset, intensity or duration of relief afforded by the aspirin. (Moertel, Tr. 6291; DeKornfeld, Tr. 8409; Banker, Tr. 12940; Feinstein, Tr. 16482; Danhof, Tr. 17269). Therefore, studies that examine the amount of drug in the bloodstream are not reliable for comparing analgesic performance of various brands of aspirin. Consumers' perceptions are not adequate because consumers cannot evaluate for themselves the efficacy of drugs. (DeKornfeld, Tr. 8421) The reason for this is that consumers' expectations regarding drug performance play a powerful role in influencing the response to drugs. (Feinstein, Tr. 16289) Indeed, this "placebo effect" may produce pain relief in 40–50% of the subjects in controlled tests who receive pharmacologically neutral substances. (Feinstein, Tr. 16322) Finally, the pain for which aspirin is taken is normally self-limiting—it will disappear regardless of what drug is taken. Thus, for these reasons, it is necessary to conduct well-controlled clinical studies in order to establish the superiority of a given brand of aspirin.

Respondent argues that although clinical tests are necessary when comparing different drugs, experts would not use controlled clinical trials to compare different formulations of the same drug. In support of this, respondent cites testimony of both Drs. Feinstein and Fields. Sterling also contends that no expert would ever recommend using a controlled clinical trial to compare different formulations of the same

drug because that would be akin to using a jet airplane to cross the street—"theoretically possible, but hardly the most efficient or sensible way to travel." (R.A.B. pp. 25–27) For this reason, respondent contends that the pharmaceutical evidence it has presented (evidence regarding rates of dissolution, etc.) can establish Bayer's therapeutic superiority. Nevertheless, the expert testimony in this case shows that at this time the consensus of experts would require clinical tests to establish the comparative superiority of any mild analgesic, even to substantiate the superiority of one brand of aspirin over another.

The reason that nonclinical evidence (such as a blood level study) is inadequate to establish comparative superiority was explained by Dr. Moertel: **[26]**

> We simply do not know at this point in time what value, if any, blood level studies have in determining comparative efficacy of mild analgesics because the studies to determine the correlation between blood levels and therapeutic effectiveness have simply not been conducted. . . . [R]ight now we do not know whether, for example, a high quick peak is good or bad in getting the most ideal therapeutic effect from salicylates because these studies have never been conducted. (Tr. 6291–92)

Dr. DeKornfeld held the same belief and stated, "I don't believe that blood levels can be directly translated at any time into establishing clinical effectiveness, unless clinical effectiveness is also measured independently." (Tr. 8409) He also stated that there is "very little, if any" relation between either the product formulation or pharmaceutical quality (size, shape, manufacturing process, presence of substances other than active ingredients) and the therapeutic superiority of any mild analgesic which meets the requirements that permit it to be marketed in this country. (Tr. 8414–15) Dr. DeKornfeld gave his opinion that the 223 Study (CX 448), a study which compared Bayer with 220 other brands of aspirin, could not be used to draw any conclusion regarding the therapeutic superiority of Bayer because it compared only physical and chemical characteristics and differences in those characteristics were not likely to have an impact on clinical effectiveness. (Tr. 8415–16)

An analysis of the testimony of respondent's experts shows that they, too, recognized the value of and need for well-controlled clinical tests. Dr. Feinstein agreed that the amount of a drug present in the blood is not well correlated with clinical analgesia. (Tr. 16413) He also conceded that there was not a high correlation between comparisons of pharmaceutical characteristics and clinical analgesia (Tr. 16415), and that in the absence of clinical trials he would have no way of saying that one drug was better than another (Tr. 16417). He did indicate that in some instances doctors must choose between two drugs (or between two brands of the same drug) and that in making

that sort of decision a doctor will use whatever evidence is available to make that choice even though the evidence might not demonstrate therapeutic superiority. (Tr. 16425–27) However, all that the doctor could then feel confident of would be that the chosen drug was equal to the one not selected. Whether or not it was superior could only be determined with clinical evidence. (Tr. 16427)

The other expert with experience in testing who testified for respondent was Dr. Fields. Respondent cites his testimony in support of the proposition that clinical tests are not necessary when comparing two formulations of the same drug. (R.A.B. p. 27) However, Dr. Fields has no experience in the testing of mild analgesics and his testimony cited by respondent related to a study in which he participated that measured aspirin's [**27**] effectiveness in preventing clotting and lowering the risk of stroke. Prior to conducting this study, a brand of aspirin had to be selected to administer to participants. Based upon nonclinical evidence (including the 223 Study, CX 448) Bayer was selected. Dr. Field's testimony makes it clear that the considerations of the scientists conducting the study were peculiar to the study. For example, they were concerned about factors which might tend to prevent double blinding and about whether the manufacturing process would encourage the decomposition necessary to prevent coagulation. (Fields, Tr. 16590, 16596) Although these considerations might be important in selecting an aspirin to test on potential stroke victims, they are not relevant to establishing the therapeutic superiority claimed by Sterling for Bayer.

Sterling also attempts to rely for support on several scientific articles which it contends indicate that experts do not require clinical tests when comparing two formulations of the same drug. (R.A.B. p. 27) But respondent's own expert, Dr. Feinstein, admitted that both of the articles cited by respondent were generally quite positive about the importance of well-controlled clinical trials and that the point of those articles was that clinical trials must be done carefully. (Tr. 16472–73)

The evidence in this case also shows that in the past Sterling demanded that its competitors rely on clinical studies to support their comparative claims. In 1970, in response to advertisements by Bristol-Myers claiming superiority for Excedrin, Sterling's advertising agency wrote on Sterling's behalf to the television network and argued that such superiority claims should not be made unless substantiated by well-controlled clinical tests. (CX 347C-E) Although it is true that Excedrin has a different formula than aspirin, Sterling requested that the same clinical test standard be imposed on other marketers of analgesics who claim superiority over aspirin for any analgesic differing in any way from the standard aspirin tablet. This request was

made again in 1974 by Dr. Monroe Trout, the Senior Vice President and Director of Medical Affairs for Sterling. In an appearance before the FDA's OTC Analgesics Panel, he suggested, "... that OTC analgesic products containing aspirin, *with or without additional ingredients*" disclose on their labels that the product is not superior to two 5-grain aspirin tablets "unless the superiority claimed or implied by such variance is adequately established by well-controlled studies of pain relief, anti-pyresis, anti-inflammatory or side effects." (CX 456M; emphasis added) Dr. Trout made clear in his statement that the same clinical testing requirement should be imposed upon a manufacturer claiming superiority for an analgesic that was merely a larger-than-normal dose of aspirin. (CX 456M) Thus, Sterling would have required its competitors to perform clinical tests to establish the superiority of one analgesic containing only aspirin over another analgesic containing only (albeit a lesser amount of) aspirin. **[28]**

Respondent objects to these references to its prior statements and contends that the ALJ has used them to estop Sterling from asserting a different position in this case. (R.A.B. p. 31) We do not believe that statements made by Sterling in the past prevent it from expressing different views in this case. However, Sterling's prior statements do provide evidence of the fact that scientists involved in the manufacture of analgesics require well-controlled clinical studies to establish superiority. These statements also show that Sterling was aware of the significance of clinical testing. Thus, we find that Sterling's prior statements are relevant and probative of the need for clinical tests to establish Bayer's superiority.

Respondent argues that it would be inconsistent with FDA policy to hold that nonclinical evidence does not constitute a reasonable basis for its claims. Further, it argues that in some instances the FDA will permit a drug to be marketed based solely upon pharmaceutical studies. Respondent has cited several examples of drugs which were qualified by the FDA as safe and effective even though no clinical studies were submitted. (R.A.B. pp. 37–42) It is true that the FDA would permit some internal analgesics to be marketed without any clinical testing. (45 FR 77807–08, Nov. 24, 1980) However, these are analgesics whose ingredients are identical to some other drug on the market which has already been proven safe and effective with clinical studies. If it can be shown that the new drug ("generic") is absorbed into the body at basically the same rate and to the same extent as a drug already on the market, the new drug will be assumed equally safe and effective as the drug already on the market. Differences in the rate or extent of absorption are regarded as significant only if they "would result in therapeutic failure or hazard to the patient." 42 FR

1626, January 7, 1977.[36] Thus, this nonclinical evidence is only used by the FDA to support a conclusion that drugs are *equivalent,* not that one is superior to another. Indeed, the FDA Commissioner expressed the belief that if two drugs are manufactured in compliance with good manufacturing practice, if they contain identical amounts of the same active ingredients and if they do not present any problems regarding rate or extent of absorption, then it is reasonable to assume that the drugs are of equal efficacy. 42 FR 1625, January 7, 1977. This statement basically echoes the comment of Dr. Feinstein that nonclinical data could lead to a conclusion that two brands of aspirin are at least equally effective. (Tr. 16427) **[29]**

Although the F.D.A. has never directly considered superiority claims for aspirin, it did consider a somewhat analogous issue. The F.D.A. OTC Analgesics panel was presented with nonclinical evidence regarding buffered aspirin which showed that it was absorbed into the bloodstream more rapidly than unbuffered aspirin. (This is similar to the blood level data submitted in this case by Sterling to justify its claims of Bayer's superiority.) Despite this evidence, the panel stated that no conclusion could be drawn regarding whether buffered aspirin provides more rapid relief, greater relief or more prolonged relief than unbuffered aspirin. 42 FR 35470, July 8, 1977. Thus, the FDA panel believed that blood level data could not be used to determine the comparative superiority of buffered aspirin and that controlled clinical studies were necessary to support claims of superiority. Therefore, our determination that two well-controlled clinical studies would presently be required by experts to establish Bayer's superiority over other brands of aspirin is in no way inconsistent with FDA policy or regulations.

Finally, respondent argues that it would not be feasible to conduct a well-controlled clinical study comparing Bayer with all other brands of aspirin because there are more than 200 other brands and such a test would be prohibitively expensive. (R.A.B. pp. 27–28) It also argues that it would not be ethical to conduct such a clinical trial because it would not provide a clear benefit compared to the risk of the study. (R.A.B. p. 34) However, Dr. Feinstein's testimony indicates that it would not be necessary to test all brands of aspirin in a well-controlled clinical trial in order to establish therapeutic superiority. Pharmaceutical tests could be conducted of all brands of aspirin (as Sterling has already done). Then a clinical trial could be performed on two or three of the brands in order to demonstrate whether pharmaceutical differences correlate with therapeutic differences. This sort of scheme could clinically prove superiority and would be feasible. (Fein-

[36] *See U.S. v. Generix Drug Corp.*, 51 L.W. 4282 (1983), which restricts the number of generic drugs that can be marketed without new drug applications.

stein, Tr. 16462–63) Dr. Feinstein also felt that this sort of testing scheme would overcome any ethical barriers that might block a large-scale clinical study of analgesics. (Feinstein, Tr. 16462)

Thus, it is the consensus of the experts with experience in comparing analgesic efficacy who testified in this proceeding that at this time well-controlled clinical tests are necessary to establish the comparative superiority of one brand of aspirin over others. We emphasize that we are not attempting to decree what constitutes scientific establishment because this standard may change with time. Indeed, we recognize in this case, as we recognized in *Bristol-Myers,* slip op. at 69 [102 F.T.C. at 373], that relevant experts might, in some instances, regard a proposition as established even if the clinical tests do not meet all of the criteria set out above. But, as we discuss below, the substantiation possessed by Sterling was plainly inadequate to substantiate the claims it made regarding Bayer's superiority. **[30]**

The record in this case does contain the results of one well-controlled clinical study comparing Bayer with other analgesics. That is the Lasagna-DeKornfeld Study conducted by Drs. Louis Lasagna and Thomas DeKornfeld (who testified for complaint counsel in this proceeding).[37] Its results were published in 1962 in the *Journal of the American Medical Association.* The study was randomized, placebo controlled, and double-blinded. According to Dr. Robert John who was medical director of respondent's Glenbrook Laboratory from 1971–1974 (and who testified for complaint counsel), respondent was aware of the study (John, Tr. 5546–47). Furthermore, respondent relied on the study to support advertising claims made to the public and to support complaints to the FTC concerning competitors' advertising. (Admissions 713, 714 in CX 678)

The Lasagna-DeKornfeld Study tested the analgesic performance of five OTC analgesics. Two of the five analgesics tested, Bayer and St. Joseph's, were plain 5-grain aspirins. The other three, Anacin, Excedrin and Bufferin, were combination products. Doses were administered to test subjects suffering pain and then the amount of pain relief received by each subject was recorded at seven time intervals after administration. After examining the results of the study, it was the conclusion of respondent's expert Dr. Feinstein that the study did not show any difference in therapeutic effectiveness between any of the products tested. (Tr. 16397) Indeed, Dr. Feinstein agreed that the Lasagna-DeKornfeld Study did not indicate any clinically important difference between Bayer and St. Joseph's aspirin, and when asked which of the two brands he would choose, Dr. Feinstein indicated that he would select the cheaper. (Tr. 16438) The Lasagna-DeKornfeld

[37] This study was undertaken in 1960 at the request of the F.T.C. in order to evaluate superiority claims made in advertising for each of the tested analgesics. (DeKornfeld, Tr. 8332)

Study is significant because it shows that it is possible to conduct a well-controlled clinical study comparing different brands of aspirin. It is also the only such study introduced in this case and it failed to demonstrate a clinically significant difference between the brands tested. Thus, it clearly has not been established that Bayer is therapeutically superior to all other brands of aspirin.

2. Establishment of Cope's superiority.

The other establishment claim made by respondent was that Cope is more effective than any other nonprescription internal analgesic for the relief of nervous tension headaches. Respondent does not dispute that well-controlled clinical tests are necessary to establish the therapeutic superiority of one drug over a different drug. In fact, in its brief, respondent quotes a statement [31] from its expert, Dr. Feinstein, that pharmacokinetic information cannot be used to compare two different drugs. (R.A.B. p. 26) However, the clinical evidence that respondent has submitted is inadequate to establish that Cope is superior to other OTC internal analgesics for the relief of nervous tension headache.

First, respondent has submitted evidence regarding the contents of a Cope tablet.[38] Sterling contends that the larger amount of aspirin in Cope (842 mg. compared to 650 mg. in a standard dose) necessarily provides increased analgesia. None of the studies submitted by respondent actually compare Cope's dose of aspirin with a standard dose. Furthermore, the Parkhouse Study discussed by respondent's witness, Dr. George Goldstein, demonstrated no statistically significant difference between aspirin dosages of 600 mg. and 1200 mg. (Tr. 15614) This finding is in accord with the conclusion of the FDA's OTC analgesics Panel which stated that:

> [T]here are no data available to show that multiple dosages greater than 650 mg. will provide any greater clinical benefit for analgesic and antipyretic effects. 42 FR 35364, July 8, 1977.

Thus, the mere fact that Cope has a greater than normal amount of aspirin does not establish its superiority.

Respondent has also submitted four clinical studies conducted on Cope. Only two of those compared Cope with other analgesics. (The other two compared different versions of Cope's formula with a placebo only and therefore cannot establish Cope's superiority.) Of the two remaining studies, the first compared Cope with aspirin. In this study the formulation of Cope differed slightly from the marketed version.

[38] A Cope tablet contains 421 mg. of aspirin, 32 mg. of caffeine, 50 mg. of magnesium hydroxide, 25 mg. of aluminum hydroxide gel, and 12.5 mg. of methapyrilene fumarate. (F. 799)

(Moertel, Tr. 6342) The study does not employ a placebo control so it is impossible to evaluate the sensitivity of the testing procedure. (Moertel, Tr. 6344) In addition, in the course of performing the study, the investigators changed their method of statistical analysis when they discovered that as originally designed their study would not demonstrate any difference between Cope and aspirin. Complaint counsel's witness, Dr. Moertel, an expert in analgesic testing, referred to this as "a gross and obvious example of statistical manipulation, and this is simply not acceptable scientific methodology." (Tr. 6345–46) Dr. Moertel noted that by changing methods of analysis, the investigators were able to generate results for some parameters that showed Cope to be superior to aspirin. [32] (Tr. 6348) However, because of the numerous flaws in the study, Dr. Moertel concluded that the study did not provide any evidence to establish that Cope is superior to aspirin and "certainly offers no evidence that it is superior to all other analgesics." (Tr. 6348)

Dr. Moertel also reviewed the other clinical study, which compared Cope with Anacin, and it was his conclusion that "this study offers very strong evidence that there is no difference at all between Cope and Anacin, and offers no evidence of any superiority of Cope over any other marketed analgesic." (Tr. 6349) He based this opinion upon the fact that this study contained the same flaws as the study comparing Cope with aspirin (different formulation tested, no placebo control, shift in analytical techniques). (Tr. 6349–50) Also, in this study, there was no significant difference for any of the parameters analyzed. (Tr. 6350)

Our examination of the ads in this case shows that respondent made claims of established superiority for Bayer and for Cope. The evidence shows that, in fact, relevant experts would not regard either product as having been established as superior. Therefore, respondent's advertised claims are false.

3. Bayer's superior pharmaceutical quality.

In addition to the claims of established superior efficacy which Sterling made for Bayer and Cope, Sterling also represented that it had tested Bayer against 220 other brands of aspirin and that this test demonstrated that Bayer was superior to the other brands with respect to quality, purity, freshness, stability, and speed of disintegration. Although grouped apart from the other establishment claims, these claims, alleged in paragraphs 20 and 21 of the complaint are, in fact, akin to establishment claims because the advertisements claim that Bayer's superior qualities were demonstrated by the test comparing it with 220 other brands. In the previous sections of this decision, we have found that experts require claims of superior effica-

cy to be substantiated with well-controlled clinical tests. However, Sterling contends that claims of superior manufacturing quality may be substantiated with various chemical and sensory tests.[39]

In 1968 Sterling conducted a test entitled, "Quality Comparison of Bayer Aspirin and Competitive Aspirin Products of the American Market," (the "223 Study") which compared Bayer with 220 other brands of aspirin and aspirin-based analgesics. In this test, 30 different **[33]** product attributes were tested by nonclinical means. Several of the attributes tested were related to purity, freshness, stability, and speed of disintegration. Sterling claims that this study substantiates its claims related to Bayer's quality. However, the ALJ concluded that this test did not demonstrate that Bayer was purer, fresher, more stable, or quicker to disintegrate than the other brands tested. Furthermore, he concluded that the test did not demonstrate that Bayer was superior in overall pharmaceutical quality to the other tested brands. From these conclusions respondent has appealed. (R.A.B. pp. 51–56)

Sterling argues that the ALJ's analysis of the 223 Study is invalid and that it is improper to examine specific pharmaceutical parameters in isolation. It contends that the 223 Study should be used only to make a judgment regarding overall pharmaceutical quality. (R.A.B. pp. 43, 56, 85–86) Although it may originally have been Sterling's intent to use the 223 Study only to reach a conclusion regarding pharmaceutical quality, its ads represent much more than that. Consumers could reasonably interpret the ads discussed above (pp. 8–14) to indicate that Bayer had been compared to 220 other brands and that the tests showed Bayer to be purest, freshest, most stable, and quickest to disintegrate.[40] Thus, it is valid to examine the individual attributes tested in the 223 Study to determine whether that evidence supports the specific claims made in the ads.

First, a facial examination of the evidence shows that Bayer is not quicker to disintegrate than all other tested brands of aspirin. Two of the thirty tests in the 223 Study involved speed of disintegration. The results (CX 430A, B) show that all tested samples of Bayer passed both tests. But so did all tested samples of at least 22 other brands.[41] Thus, with respect to speed of disintegration, it is impossible to conclude that the 223 Study shows Bayer to be superior to all other tested brands. In addition, Sterling also had in its possession several other

[39] As we noted above (*supra* pp. 11–12) claims of pharmaceutical (or manufacturing) quality are linked to and often imply therapeutic quality. However, if appropriately qualified, an ad may make a claim solely regarding such characteristics not directly related to therapeutic quality.

[40] Not every ad which mentioned a tested attribute necessarily implied that Bayer was superior with respect to that attribute. In some ads, attributes were mentioned only as examples of the tests performed to demonstrate Bayer's superior overall quality. *See* CX 48.

[41] Among the brands that disintegrated as rapidly as Bayer were McKesson, Norwich, Parke-Davis, Rexall, and St. Joseph. (CX 430 A)

studies of rates of tablet disintegration which show that some other brands disintegrate as rapidly as Bayer. (F. 634, 645)

The results of the 223 Study also do not show that Bayer is purer than all other tested brands of aspirin. Expert witnesses testified that an aspirin tablet may contain a veritable alphabet soup of impurities including FSA, ASAN, ASSA, and SSA (substances whose full names are free salicylic acid, aspirin anhydride, acetylsalicylsalicylic acid, and salicylisalicylic acid; *see* Rhodes, Tr. 11159; Falliers, Tr. 13346, 13361, 13363). [34] The 223 Study only tested for one of those impurities, FSA. Two of the thirty tests measured the level of FSA in the various brands. All of the tested samples of Bayer passed one of the FSA tests but one Bayer sample failed the second test. However, all tested samples of Parke-Davis and Safeway brands passed both of the FSA tests. Thus, the 223 Study does not show that Bayer is the purest of all brands tested.

Some Bayer ads also represented that Bayer was the most stable of all brands tested. According to the charts reporting the results of the 223 Study (CX 430A, B), five of the thirty tests measure product stability (*i.e.,* tendency to decompose). Since FSA is created when aspirin decomposes, the two tests measuring the presence of that impurity measure the extent of decomposition. Also relevant (according to the charts) are tests to determine if tablets are off-color, have acetic odor, and if the cotton wadding in the bottle has decomposed. The results of the 223 Study show that no Bayer samples had acetic odor, were off color or had decomposed wadding. However, as indicated above, the Bayer samples were unable to pass one of the tests for FSA content. The Parke-Davis sample tested passed all five tests. In addition, according to the testimony of respondent's witness, Jerome Winig, a chemist who was involved in the manufacture of Bayer aspirin for more than 40 years (I.D. pp. 50–51), acetic odor and off-white color may be caused by the manufacturing process and may not be an indication of decomposition. He testified that a test for the presence of FSA is a much more accurate measure of decomposition. (Tr. 14231, 14242) Examining test results for FSA levels, both Parke-Davis and Safeway brands performed better than Bayer. Thus, the 223 Study did not demonstrate that Bayer was the most stable brand tested.

Although Sterling's ads claimed that Bayer had been tested against 220 other brands of aspirin and been found the freshest, "freshness" does not appear to have been a product attribute specifically tested in the 223 Study. An examination of the 223 Study results shows that no test or group of tests is listed as a test of freshness. Indeed, Dr. Rhodes, respondent's expert in the formulation of drugs stated that "freshness" is not a technical term used in the industry and that it

is just an imprecise "layman's term." (Tr. 11441) Nonetheless, he believed that the 223 study did test for freshness because it tested "the odor of the tablet, the amount of FSA present, the appearance, the integrity of the seal." (Tr. 11442) Dr. Rhodes stated that in his opinion the 223 Study showed Bayer to be superior. As we indicated above, there are four tests related to FSA, tablet odor and appearance. Bayer and Safeway passed three of those tests and Parke-Davis passed all four. While one might dispute whether integrity of the seal directly relates to freshness, two of the thirty tests evaluated how well the tested products were sealed. Bayer, Safeway, and Parke-Davis [35] each passed and failed one test. Consequently, even according to the criteria which Dr. Rhodes used to determine freshness, Bayer appears to be no fresher than at least two other brands tested in the 223 Study.

Does the 223 Study demonstrate that Bayer is superior in overall pharmaceutical quality to the other 220 brands tested? That is the final issue presented by paragraphs 20 and 21 of the complaint. Sterling argues that Bayer performed better overall than any other brand in the 30 tests that composed the 223 Study. Since Bayer samples failed only five of the 30 tests and every other brand failed more, Sterling contends the study demonstrated that Bayer is the superior quality aspirin. The ALJ did not agree. He determined that, for several reasons, the 223 Study was inadequate to demonstrate Bayer's superior quality. First, the protocol was not adequate. (F. 1164) Second, there were inadequate records of the means used to collect and handle the samples tested. (F. 1166) Third, the study failed to control for the age of samples. (F. 1168) Fourth, a Sterling employee selected the parameters to be tested. (F. 1169) Fifth, all tests, including unblinded sensory tests, were conducted by Sterling employees. (F. 1170) Sixth, Bayer samples were transported by a different means than other samples. (F. 1174) Seventh, some of the Bayer samples came from Sterling's warehouse and not from the store shelves. (F. 1175) Eighth, some minor brands were grouped together in a somewhat arbitrary fashion. (F. 1177) Ninth, there were no tests for statistical significance of demonstrated differences. (F. 1179) In addition to these methodological flaws, the ALJ noted that Bayer was not superior to all other brands in all respects tested. (F. 1179) Thus, he determined that the 223 Study was not capable of demonstrating qualitative superiority.

Respondent objects to this conclusion and argues that the ALJ's reasoning was not supported by expert testimony. It notes that Sterling's experts uniformly agreed that the 223 Study showed Bayer to be qualitatively superior but that none of complaint counsel's experts testified to flaws in the study. (R.A.B. pp. 51–56) Complaint counsel concede that none of their experts testified regarding the 223 Study

but they contend that the study fails to meet standards required by relevant experts. Complaint counsel contend that these standards were derived from the expert testimony of Sterling's own witnesses. (C.An.B. p. 36) [36]

It would, of course, be possible for complaint counsel to meet its burden of proof on this issue by showing that the 223 Study did not live up to standards set forth by respondent's experts. Thus, it is not essential that complaint counsel present testimony from their own experts on every issue. However, after considering the arguments of counsel and the testimony, it does not appear to us that complaint counsel have been able to meet their burden of proof on this issue. For example, complaint counsel quote testimony from respondent's experts to show that nonclinical tests must be subjected to statistical analysis. (C.An.B. pp. 37–38) Specifically, they cite testimony from Drs. Horner, Feinstein, Danhof, and Banker. Yet, an examination of the testimony cited shows that in no instance does it truly apply to the 223 Study. Dr. Horner noted that in general it is important to test for statistical significance (Tr. 10850), but he did not indicate that the results of the 223 Study lacked statistical significance. Dr. Feinstein stated that in evaluating clinical studies, it is important to test for statistical significance. (Tr. 16428) But he did not indicate that the same sort of statistical analysis should be applied to the sorts of tests conducted in the 223 Study. The portion of Dr. Danhof's testimony cited by complaint counsel discussed a study of gastric bleeding in which no statistically significant differences had been shown. (Tr. 17241–42) Dr. Danhof did not mention the 223 Study. Finally, in his testimony, Dr. Banker stated that if a study shows a large difference, a test for statistical significance may not be necessary. Only when small differences are demonstrated must they be tested for statistical significance. (Tr. 12904–05) Dr. Banker does not indicate whether the differences demonstrated in the 223 Study were large or small.

Other testimony regarding other alleged flaws cited by complaint counsel also suffers the same problem—it is not clearly related to the 223 Study. The testimony adduced by complaint counsel from respondent's experts was of a general nature. None of those experts indicated that the 223 Study was flawed or that conclusions should not be drawn from it. Thus, although the shortcomings of the 223 Study might prevent it from demonstrating Bayer's superior quality, we do not think that complaint counsel have met their burden of proof on this issue. [37]

C. *The Substantial Question Issue.*

Paragraph 12 of the complaint restates four superiority claims

which respondent made regarding Cope and Vanquish.[42] Paragraph 13 alleges that a substantial question as to the validity of these claims exists among experts. Then paragraph 14 charges that even in those instances in which the ads did not indicate that the claims had been established, the failure to disclose the existence of the substantial question rendered the ads deceptive. The ALJ found the ads deceptive and entered an order provision which would require respondent to substantiate every comparative performance or freedom from side effects claim with a type and quantity of evidence necessary to establish the claim among experts. If that degree of substantiation was lacking, the ALJ's order would require respondent to disclose in the ad the existence of a substantial question as to the claim's validity. However, as our decision in *Bristol-Myers* indicates, slip op. at 38–44 [102 F.T.C. at 348–355], we no longer endorse the substantial question theory of liability. For reasons set forth in that decision we dismiss all the allegations of paragraphs 12–14.[43] **[38]**

D. *Lack of a Reasonable Basis*

Unlike *American Home Products* and *Bristol-Myers,* the complaint in this case alleges that for certain of its comparative performance claims, Sterling lacked a reasonable basis. Specifically, paragraph 10 of the complaint alleges that Sterling claimed Bayer is therapeutically superior to any other aspirin and that Bayer Children's Aspirin is therapeutically superior to any other children's aspirin. Paragraph 11 alleges Sterling lacked a reasonable basis for those claims. As we indicated above, our examination of the challenged advertisements in this case did not reveal any ad in which Sterling represented that Bayer Children's Aspirin was therapeutically superior to other brands (*supra* pp. 15–16). Furthermore, all advertisements which represent that Bayer is therapeutically superior to other brands also represent that Bayer is therapeutically superior to other brands also represent that Bayer's superiority has been established (*supra* pp. 12–13).[44] For that reason, we have considered the amount of support necessary to establish these claims among members of the relevant

[42] The four comparative claims are: (1) Cope is a more effective reliever of "nervous tension headache" than any other OTC internal analgesic; (2) Vanquish is a more effective pain reliever than aspirin or buffered aspirin; (3) Vanquish will result in less stomach discomfort than any unbuffered OTC internal analgesic; and (4) Vanquish is a more effective pain reliever than the largest selling "extra strength" tablet. As we discussed in part A, respondent's ads made all four of these claims.

[43] Application of the substantial question theory would require a conclusion that consumers expect the same level of support for a claim regardless of whether Sterling represents the claim has been established. Had complaint counsel presented evidence showing that consumers held such a belief—*i.e.,* that consumers believed that all superiority claims were scientifically established—then the failure to disclose the lack of evidence establishing such claims might well have been deceptive. However, as in *Bristol-Myers,* no evidence of consumer beliefs was presented here.

[44] We therefore find it unnecessary to decide whether the evidence Sterling had would have been sufficient to provide a reasonable basis for an unembellished superiority claim (*i.e.,* one not representing that superiority had been scientifically established).

scientific community. In determining whether respondent possessed a reasonable basis to support these very same claims, we must apply the same standard. According to *Pfizer,* one of the factors to consider in determining whether an advertiser possesses a reasonable basis to support a claim is the nature of the claim. 81 F.T.C. at 64. Since Sterling has represented in its ads that Bayer's superiority has been established, it could not have a good faith belief in the truth of that claim unless adequate evidence existed to establish Bayer's superiority. Thus, in this instance, the reasonable basis approach requires the same level of support as the establishment theory. Since we have already determined that Bayer's superiority was not established, we therefore also find that Sterling lacked a reasonable basis for this claim.

III. TENSION RELIEF CLAIMS

Paragrah 15 of the complaint in this case alleges that Sterling represented that Bayer, Cope and Midol relieve nervous tension, stress, fatigue and depression. Paragraph 16 charges that Sterling lacked a reasonable basis for these claims. The ALJ found that respondent made the claims without a reasonable basis and he entered an appropriate order provision. We agree with respect to the claims for Cope and Midol, but disagree with respect to the claims for Bayer. **[39]**

A. *The Advertisements.*

The ALJ cites ten ads which represent that Cope relieves tension.[45] Each of these ads presents Cope as a product especially designed to relieve nervous tension headache, and each ad indicates that Cope has an ingredient that relieves pain and an ingredient that relieves nervous tension. For example, CX 273 states:

> This is the most common headache there is, the nervous tension headache. As you can see, it's a two fold problem. Nervous tension and pain. For relief, try the two fold approach you get with Cope. Cope alone of all the leading headache remedies you can buy gives you a powerful pain reliever plus a proven relaxer. . . .

The implication of this ad is that a nervous tension headache is a combination of two problems, tension and headache. Cope is represented as having an ingredient to cure each of these problems. Thus consumers could reasonably infer that if they were tense, they could take Cope because one of Cope's ingredients is specifically intended to relieve nervous tension. The other nine ads cited by the ALJ make a similar representation.

[45] CX 272-276, 283, 287, 292-294.

The ALJ found that 17 ads for Midol represent that it relieves nervous tension. (F. 390) We agree with respect to 16 of those ads.[46] In all of these ads, Midol is presented as a product that relieves menstrual cramps. In addition to relieving cramps, each of the ads also represents that Midol can cure a number of other ills. For example, CX 296A states:

> Midol goes to work fast to help relieve a woman's discomforts. Like low backache, headache, calms jumpy nerves too. And the over all action of Midol chases the blues away.

CX 306Z035 indicates that Midol will "soothe irritability" and CX 306Z037 states that Midol contains "a special mood-brightener that gives you a real lift." In CX 306B, a woman is described as tense before she takes Midol and happy afterwards. All of these ads represent that Midol will relieve tension ("calm jumpy nerves," "soothe irritability") and most of them also portray [**40**] Midol as able to relieve depression because it is a "mood brightener." Thus, respondent did represent that Midol relieves tension, depression and stress.

Finally, the ALJ determined that five advertisements for Bayer represent that it will relieve tension (CX 29, 30, 33, 141, 151). Although it is a close call, we find that complaint counsel have not met their burden of showing that any of these ads represents that Bayer will relieve tension. Typical of these ads is CX 30. It is a television ad which shows a mother on a hot summer day attempting to tend numerous noisy neighborhood children in a backyard pool. As the scene progresses, the mother becomes more fatigued and irritable. The announcer states:

> As the day wears on, "Hot Weather Headache" can make you tense, irritable, out of sorts. And that's when Bayer works wonders. . . . Take two Bayer tablets and put your feet up. In just minutes, headache's gone.

At the close of the ad, the mother appears refreshed and happy. Although this ad does mention tension and does depict a potentially tension provoking scene, the message of the ad appears to be that the hot, hectic day gives the mother a headache and the headache, in turn, makes her tense. The ad then states that Bayer will relieve the headache. The implication is that headache relief causes the tension to disappear.

We considered a somewhat similar ad in *Bristol-Myers*. In that case, CX 53 depicted a tense confrontation between a student and a college dean. The audio portion of the ad stated that Bufferin provided relief from headache. We ruled that CX 53 did represent that the product

[46] CX 296A, 297–300, 306, 306A-C, 306R, 306Z005, 306Z011, 306Z035, 306Z037, 306Z041, 306Z045, 306Z053.

would cure tension, but in that case we had copy tests showing that more than 50% of viewers received the impression Bufferin relieved tension. In this case, since the claim is not apparent to us from a careful examination of the ads, we are unwilling in the absence of extrinsic evidence to find that consumers infer from these ads that Bayer will relieve tension. No extrinsic evidence was presented and therefore we find that Sterling did not represent that Bayer relieves tension.

B. *Evidence on Tension Relief.*

Cope and Midol both contain aspirin. In addition, Cope contains buffers, caffeine and an antihistamine, methapyrilene fumarate. Midol contains (in addition to aspirin) caffeine and an antispasmodic, cinnamedrine hydrochloride. Sterling has presented no evidence indicating that caffeine, buffers or [41] cinnamedrine hydrochloride produce any tension relieving effect and there is expert testimony confirming that none of these three ingredients relieves tension. (Rickels, Tr. 7974, 8019, 8021). Indeed, caffeine, an ingredient in both Cope and Midol is contraindicated for the relief of tension. (Rickels, Tr. 7974) However, respondent did present evidence that aspirin and methapyrilene fumarate have tension relieving properties, and it is to that evidence we now turn.

The evidence presented by Sterling regarding its tension-relief claims must be considered in light of the factors set forth in *Pfizer* for determining what constitutes a reasonable basis. The ads at issue here advise consumers to take aspirin-based analgesics for the relief of tension. If the products cannot provide that relief, then consumers may forego effective remedies and are needlessly being encouraged to consume aspirin, a drug with potentially hazardous side effects. (*see* infra p. 47) Furthermore, as with other performance claims regarding mild analgesics, it is virtually impossible for consumers to verify for themselves whether the product can relieve tension. All of these considerations are relevant to determining whether Sterling's evidence constitutes a reasonable basis for its claim.[47]

As we mentioned in *Bristol-Myers,* tension can be caused or exacerbated by headache pain. Since aspirin can relieve a headache, it could relieve or lessen the tension caused by a headache. However, respondents' ads represented that Cope and Midol could relieve tension which exists independent of headache pain. Thus, the mere fact that aspirin relieves pain does not by itself support claims that aspirin has tension-

[47] Sterling appears to argue (in connection with its claims for Bayer) that the Commission is precluded from anything more than a superficial determination of a scientific test's adequacy. We disagree and will, in appropriate situations, consider evidence regarding the details of scientific tests in order to determine whether the advertiser's reliance thereon was reasonable. *See Bristol-Myers,* slip op. at 32–37 [102 F.T.C. at 343–347]; *Porter & Dietsch,* 90 F.T.C. at 870–871; *Firestone,* 81 F.T.C. at 445–449.

relieving properties. (Rickels, Tr. 8102–03)[48] [42]

To support its claim that aspirin can relieve tension, Sterling has relied on various studies and reports in medical literature. The first item was a 1965 study by Krumholtz and Merlis. This study was also submitted into evidence in *Bristol-Myers,* and once again, Dr. Rickels, complaint counsel's expert on psychopharmocology and tension, criticized flaws in the study, especially the failure of the authors to identify the symptoms of the test population. It is therefore possible that changes experienced by the test subjects resulted from the analgesic effects of aspirin. (Tr. 8115–16) Furthermore, the study was designed to measure aspirin's effect on depression rather than tension, and the authors recognized that additional study was necessary to test the tranquilizing action of aspirin. (Goldstein, Tr. 17977)

Much of the other evidence presented regarding aspirin related to its ability to overcome insomnia. However, sleeplessness can be caused by many factors other than tension. (L. Goldstein, Tr. 17900) Thus, a mere showing that aspirin has hypnotic (sleep-inducing) effects does not constitute a reasonable basis for tension relief claims unless it is shown that the sleeplessness was caused by tension. Sterling submitted a report of a 1959 study by Boyd, *et al.,* which reported that buffered aspirin had hypnotic effects. However, the record does not show that any of the insomniacs who participated in the study suffered from tension. Furthermore, the record shows that a substantial majority of subjects in Boyd's study were receiving other medication including barbiturates (a sleep-inducing drug). (Goldstein, Tr. 17981) Finally, Dr. Rickels noted that the study had methodological flaws. (Tr. 8178)

Sterling also submitted three reports from medical literature and a chapter from a 1969 textbook supporting aspirin's efficacy as a tension reliever. The three reports refer to potential sedative effects of aspirin, not to tension relief. (Goldstein, Tr. 17849, 17851, 17852) Thus, these reports do not make clear whether aspirin relieves sleeplessness caused by tension or whether aspirin relieves pain thereby permitting the subject to sleep. (Goldstein, Tr. 17983–84) References to medical texts, without more, are not given much weight by scientists. Normally, they look to the underlying data and not to the text. (Rickels, Tr. 7978) Indeed, neither the textbook reference nor the three reports contain any underlying data.

Sterling additionally offered several electroencephalagram ("EEG") studies to support its tension-relief claims. However, Dr. Rickels noted that because EEG studies are not able to directly meas-

[48] Dr. Rickels gave the following analogy to illustrate the point: A person with a bladder infection may have to urinate frequently during the night and be unable to sleep the whole night through. An antibiotic which cures the infection would permit the person to sleep the entire night but the antibiotic would not, therefore, be considered a sleeping aid.

ure a drug's ability to relieve tension, they only give a preliminary indication of what a drug can do. (Rickels, [43] Tr. 7970, 8184–85) Indeed, in some instances EEG's have indicated that a change was taking place in a subject when clinical studies have been unable to show any change. (Rickels, Tr. 8185) In addition, EEG results can be misleading because of variability among test subjects. (Goldstein, Tr. 17959–61) Respondent's witness Dr. Goldstein criticized four EEG studies submitted by Sterling (including three studies which he had conducted) based upon the failure to take variability into account. He indicated that by failing to take variability into account, he "was mixing apples and oranges and expressing their averages in terms of bananas." (Tr. 17959) The only other EEG study was conducted in 1978, long after Sterling had made the claims at issue in this case. Although the authors concluded that aspirin did improve the sleep of insomniacs, Dr. Goldstein noted that there were individual differences among the eight test subjects and that two received no benefit at all. He concluded that this was caused by the fact that the test subjects were insomniacs and there was no indication as to what the cause of each patient's insomnia was. (Tr. 17900) Finally, Dr. Goldstein conceded that the FDA would not rely solely on EEG studies to demonstrate the sedative property of a drug. (Tr. 17987)[49]

In addition to the evidence submitted by respondent, complaint counsel submitted evidence on two studies which show that aspirin does *not* relieve tension. The first was a study conducted by complaint counsel's expert Dr. Rickels in 1971 and it showed that a 500 mg. dose of aspirin (the normal dose is 650 mg.) was no more effective as a tension reliever than a placebo. (Rickels, Tr. 7951) The second study was also well-controlled, and it tested a normal dose of aspirin. It was the authors' conclusion that aspirin was not able to relieve tension. (Rickels, Tr. 8195) These studies indicate that at the time respondent was making tension relief claims for Cope and Midol, it was possible to conduct well-controlled studies measuring tension relieving capacity and that such studies showed aspirin was not a tension reliever. Furthermore, a letter from Sterling's files (CX 358) shows that as of May 1969 (prior to making most of the tension relief claims), Sterling was well aware that aspirin would not relieve tension. Thus, respondent did not have a reasonable basis for believing aspirin would relieve tension. [44]

Methapyrilene fumarate, an ingredient in Cope, is an antihistamine (a substance which combats infection). Sterling presented a variety of evidence (but no expert testimony) regarding methapyrilene

[49] In addition to the tests and studies discussed above, Sterling presented evidence designed to show that ingestion of aspirin increases the body's level of tryptophan, an amino acid which must be present at certain levels for sleep to begin. However, as explained above, producing sleep is not the same as reducing tension and thus, this evidence does not support tension relief claims regarding Cope and Midol.

(including two clinical studies). However, none of this evidence provides a reasonable basis to substantiate the tension relief claims for Cope. First, most of the participants in the two clinical studies had headaches. (F. 938) By not separating those participants who had only tension from those who had pain, it is impossible to conclude that Cope had tension relieving properties separate from its analgesic properties. (Rickels, Tr. 8007) Since the Cope ads represent that Cope can relieve this "free-floating" tension, these tests do not support those claims. The journal excerpts submitted by Sterling (F. 945) suffer from the same flaw.

Second, since methapyrilene fumarate is an antihistamine, it is also a hypnotic. However, as explained above, inducing sleep is not the same as relieving tension. Indeed, drowsiness would be undesirable, even dangerous, when produced as a side effect of a drug taken during the day. (Rickles, Tr. 8183) For that reason, eight studies submitted by Sterling demonstrating methapyrilene's sleep inducing properties do not support tension relief claims. The same is true of the bibliographic material listed in F. 946.

Finally, Sterling relied on numerous works of Dr. Arnold Friedman. Dr. George Goldstein,[50] a Sterling employee, said these articles implied that an ingredient with sedative properties is appropriate to treat tension. (Tr. 15508) However, Dr. Friedman's writings concerned the effects produced by a combination of an analgesic and a barbiturate and as Dr. Rickels, an expert in pharmacology, indicated, it would not be proper to draw any conclusions about an antihistamine (such as methapyrilene fumarate) from data regarding a drug containing a barbiturate. (Rickels, Tr. 8016)

Although respondent has presented some evidence to show that Midol will brighten a user's mood, it presented no such evidence to the FDA. In its submission, it claimed only that the ingredients in Midol would relieve menstrual pain. (George Goldstein, Tr. 15603) However, in this proceeding, respondent has claimed that the caffeine in Midol acts as a mood brightener. The claim is based in part on the testimony of Dr. George Goldstein. Dr. Tainter, another Sterling employee, disagreed and indicated that the presence of caffeine in Midol might heighten the user's pain and would, in any event, be too small a dose to affect the user's mood. (CX 417B) Also, Drs. Goodman and Gilman, who were recognized by respondent's witness Dr. George Goldstein as "among the leading lights of American pharmacology" (George Goldstein, Tr. 15590) do not list brighter mood among the [**45**] effects of a therapeutic dose of caffeine (George Goldstein, Tr. 15593–94). Final-

[50] Two Drs. Goldstein testified for respondents. Up to this point, all references have been to the testimony of Dr. Leonide Goldstein, an expert in the biological basis of human behavior (F. 121). Dr. George Goldstein was qualified as an expert only in the use of Sterling's products.

ly, the rest of the evidence presented by Sterling makes it appear that the amount of caffeine in Midol is too small to have any therapeutic effect. (Rickels, Tr. 7974; George Goldstein, Tr. 15587, 15592)

The evidence presented by respondent thus is inadequate to substantiate the mood altering claims it made for Cope and Midol. None of the evidence which Sterling presented regarding aspirin separates its unquestioned analgesia from any tension-relieving effect it may possess. Other evidence (such as EEG studies and the tryptophan theory) is inconclusive, especially in light of the well-controlled studies presented by complaint counsel which show that aspirin relieves tension no more effectively than a placebo, and the letter from Sterling's files showing that it knew substantiation did not exist for the claim that aspirin relieved tension. The evidence presented regarding methapyrilene fumarate is either not helpful because any tension-relieving effect Cope might produce was not isolated from Cope's analgesic effect, or of questionable relevance (*i.e.,* the studies regarding barbiturates). The evidence regarding the caffeine in Midol does not clearly show that caffeine can brighten one's mood and also seems to indicate that under any circumstance, Midol does not contain enough caffeine to have any effect. Thus, in light of the claims made by respondent for its products, in light of the testimony, we conclude that respondent did not possess a reasonable basis for its claims that Cope and Midol can affect a user's mood.

IV. FAILURE TO DISCLOSE THE PRESENCE OF ASPIRIN; REPRESENTATION THAT MIDOL CONTAINS OTHER THAN ORDINARY ASPIRIN

Paragraphs 23 through 25 of the complaint charge that Sterling failed to disclose in its advertising that Vanquish, Cope, and Midol contain aspirin. An examination of the challenged advertisements for these products shows that none disclose that aspirin is an ingredient. However, as we explained in *Bristol-Myers,* slip op. at 54 [102 F.T.C. at 361], we are unprepared to hold that the mere failure to disclose the presence of aspirin in advertising for aspirin-based analgesics renders that advertising materially misleading. In *Bristol-Myers,* we found that advertisements for Bufferin and Excedrin created the impression that those products did *not* contain aspirin. In light of that advertising, we held that the failure to disclose the presence of aspirin was materially misleading. In this case, there are no allegations that Sterling's advertising created the impression that Vanquish and Cope do not contain aspirin. For that reason, we find that the failure to disclose the presence of aspirin in Vanquish and Cope does not violate the FTC Act and we dismiss all charges related to Paragraphs 23 and 24. On the other hand, Paragraph 26 alleges that advertisments for Midol represented that it does not contain aspirin and caffeine. These

representations would make the failure to disclose the presence of aspirin a violation of the FTC Act. [46]

The only active ingredients in Midol are aspirin, caffeine, and an anti-spasmodic, cinnamedrine hydrochloride. Nonetheless, numerous ads for Midol do create the impression that Midol does not contain aspirin. This impression is created by ads which state that Midol and its ingredients are special and out-of-the-ordinary. For example, CX 302 states:

> Midol starts to work fast with an exclusive formula that helps stop periodic pain . . . and its medically approved ingredients gives effective relief from headache and low backache. All in all, Midol's unique formula gets you through those days in comfort.

The impression created by this ad is that Midol, and everything about it, is special and different. Its formula is described as "unique" and "exclusive." In the midst of language that creates an aura of uniqueness about the product, the ad states that Midol has a "medically-approved ingredient" to relieve pain. Consumers could reasonably infer that the "medically-approved ingredient," a part of the unique formula, is also unique. As respondent concedes, however, the "medically-approved" pain reliever is aspirin (Hartman, Tr. 9166), an ingredient," which is anything but unique or special (*see American Home Products,* 98 F.T.C. at 362), an ingredient which is familiar to most consumers. It would have been a simple matter for respondent to clarify its ads so that consumers would realize that it is the anti-spasmodic ingredient which is unique to Midol.

In another ad Midol is contrasted with "ordinary pain relievers." The ad (CX 296B) states, "An exclusive formula with medication ordinary pain relievers don't give you, Midol relieves the pain of backache, headache and other discomforts mature women can get." Although respondent contends that no other product has exactly the same formula as Midol and that ordinary pain relievers do not contain cinnamedrine hydrochloride, the ad has blurred the distinction between ingredients that relieve pain and those that perform another function. The impression created thereby is that the pain relieving medication in Midol is not contained in ordinary pain relievers. Aspirin is a common (*i.e.,* ordinary) pain reliever. Therefore, CX 296B creates the false impression that Midol does not contain aspirin.[51]

The ads cited above could reasonably mislead consumers into believing that Midol does not contain aspirin. A misleading claim or omission will violate the FTC Act only if the omitted information (in this case, that Midol contains aspirin) would be a material factor in

[51] Similar ads are CX 297, 300. On the other hand, CX 305 indicates that it is the anti-spasmodic that is not contained in ordinary pain relievers and CX 306 makes it clear that it is the anti-spasmodic that is exclusive.

a consumer's purchasing decision. *F.T.C.* v. *Colgate-Palmolive Co.*, 380 U.S. at 392. Section 15 of the FTC Act provides that an omission of fact may be material "in the light of representations made or suggested . . . or . . . with respect to [47] consequences which may result from the use" of the product. The failure to disclose the presence of aspirin is material in light of "representations made or suggested" in respondent's ads which create the impression that the pain reliever in Midol is unique. It is this false impression which would lead a consumer to look no further for a non-aspirin-based analgesic. It is this same false representation of uniqueness which would discourage a consumer from looking for a less expensive analgesic.

Expert testimony in this case explains one reason why consumers look for non-aspirin-based pain relievers. Aspirin may cause numerous side effects. According to Dr. Grossman, an expert in gastroenterology, aspirin may cause dyspepsia and gastrointestinal bleeding, and it may exacerbate or even cause ulcers. (Tr. 7471, 7479, 7720, 7722) According to Dr. Stevenson, an expert in asthma and immunology, aspirin, even in minute doses, can cause asthmatics to suffer attacks which may be severe or even life-threatening. (Tr. 1480, 1489) In addition, aspirin can cause skin reactions such as hives or swelling. (Stevenson, Tr. 1511–12)

Respondent argues that the ALJ greatly inflated the number of consumers who would suffer adverse reactions from aspirin. (Sterling Reply Brief, pp. 48–50) However, as we found in *American Home Products*, 98 F.T.C. at 367, the number of consumers who suffer adverse reactions to aspirin is significant. Immunologists generally warn all asthmatics to avoid aspirin, regardless of whether they are known to be aspirin-sensitive (Farr, Tr. 2606) and respondent concedes that there are at least two to six million asthmatics in the United States (Sterling Reply Brief, p. 50). Thus, some consumers avoid aspirin for medical reasons. For them, Sterling's failure to disclose aspirin's presence is material in the context of ads which create the impression Midol is aspirin-free.

The nondisclosure of aspirin is also material for economic reasons. At the time Sterling disseminated the challenged Midol advertising, Midol was substantially more expensive than most other aspirin-based analgesics. In fact, the *wholesale* price of Midol was twice as expensive as the *retail* price of Bayer and more than four times as expensive as the average retail price for non-Bayer aspirin. (F. 6, 11) Since Midol ads create the false impression that its pain reliever is unique and, therefore, not available in other products, consumers are not as likely to consider less expensive aspirin-based analgesics available on the market as potential alternatives to Midol. Thus, failure

to disclose aspirin's presence is material in the context of ads which imply that the analgesic in Midol is available in no other product. [48]

We also find that consumers are not already aware of the ingredients in the analgesics which they use. This lack of knowledge is demonstrated by several studies in the record including an informal study conducted by Dr. Moertel (Tr. 6355–60) and a 1970 Analgesic Segmentation Study (CX 394) performed at Sterling's request, which showed that 82% of those surveyed were unable to name any of the ingredients in the brand-name headache remedy they normally use. Sterling argues that the results of these studies do not prove that consumers are unaware of the contents of analgesics because the results are not projectible to the general population. (Sterling Reply Brief, p. 49) While it is true that these survey results may not be statistically projectible, they at least suggest that consumers are unaware of the ingredients in analgesics. (Pernica, Tr. 1998) In light of the fact that respondent has offered no contrary evidence, we are unwilling to conclude that consumers generally know which analgesics contain aspirin.

We stress that we find a violation of the FTC Act only in those instances in which Sterling affirmatively represented (either expressly or by implication) in its advertising that Midol did not contain aspirin. As we indicated in *Bristol-Myers,* slip op. at 54 [102 F.T.C. at 361], we do not find that the mere failure to disclose the presence of aspirin in advertising for aspirin-based analgesics is misleading. And, indeed, there are numerous ads in the record which do not misrepresent Midol's (or Cope's, or Vanquish's) aspirin content. These ads are silent on the subject. After viewing ads such as these, consumers would not necessarily know (based upon the ads) whether the advertised product contained aspirin. If consumers viewing these ads were concerned about aspirin content, they would have to look elsewhere for the information, but at least they would not be discouraged from doing so. On the other hand, in the context of the affirmative claims made in the Midol ads, the failure to disclose the presence of aspirin is a material omission of fact which renders the advertisement false.[52] [49]

V. COPE'S UNIQUE FORMULA

Paragraph 22 of the complaint charges that respondent falsely represented that Cope's formula is unique. The ALJ found that this representation had been made, and we agree. For example, CX 274 states:

[52] Paragraph 26 of the complaint also alleges that Sterling represented that the stimulant in Midol is not caffeine. However, the record does not contain any evidence indicating that knowledge of the presence of caffeine in an OTC analgesic is material to consumers, the ALJ made no findings on that issue, and complaint counsel have not appealed that point. Therefore, we dismiss that portion of paragraph 26 that relates to caffeine.

Cope looks different, is different. Besides a powerful pain reliever, Cope gives you a gentle relaxer. The others don't. . . . A unique formula for really effective relief of nervous tension headache. And you get it only in Cope.

CX 275 also represents that the Cope formula is "unique." These ads were shown to the public from December 1969 through March 1970. (CX 633)

The Cope ads mentioned above state that the Cope formula is unique because only Cope contains both "a powerful pain reliever" and also "a gentle relaxer." The clear message is that no other analgesic contains both types of ingredients. The ingredients in Cope are aspirin, caffeine, methapyrilene fumarate, and two antacids. Thus, the "powerful pain reliever" is aspirin and the "gentle relaxer" is methapyrilene fumarate, an antihistamine which, as explained above (*supra* p. 44) produces drowsiness. At the same time as Sterling was advertising Cope, Bristol-Myers was promoting Excedrin P.M., an OTC analgesic which contained, among other things, both aspirin and methapyrilene fumarate. (CX 357B; *see also Bristol-Myers,* slip op. at 50. [102 F.T.C. at 358]) Thus, Excedrin P.M. also contained the "powerful pain reliever" and the "gentle relaxer." Furthermore, the evidence shows that at the time Sterling was advertising that only Cope contained a "powerful pain reliever" and "a gentle relaxer," it was aware that Bristol-Myers was marketing Excedrin P.M. (CX 678 Admission 1069) and it was aware that Excedrin P.M. contained aspirin and methapyrilene fumarate. (CX 357) Therefore, advertisements that portrayed Cope as unique were false and misleading. As explained in Part IV above, such false representations of uniqueness are material because they discourage consumers from shopping for potentially less expensive alternatives.

VI. INCONSISTENT CLAIMS

Paragraph 17 of the complaint charges that respondent made several mutually inconsistent claims for its products. Specifically, it charges that respondent claimed in its ads that: (1) Bayer is as effective for the relief of headache pain as any **[50]** other OTC analgesic, and Vanquish is a more effective reliever of headache pain than aspirin; (2) Bayer will cause stomach upset no more frequently than any other OTC analgesic, and Vanquish will cause less stomach upset than unbuffered aspirin; and (3) Bayer is as effective a reliever of nervous tension headache as any OTC analgesic, and Cope is more effective for the relief of nervous tension headache than any other OTC analgesic. Paragraph 29 charges that the making of inconsistent contemporaneous claims is unfair or deceptive. The ALJ disagreed and dismissed paragraph 17 and that portion of paragraph 29 that

relates to inconsistent claims. From this determination, complaint counsel have appealed.

Complaint counsel's argument is based upon the Commission's decision in *Pfizer.* They argue that in order to substantiate advertising claims *Pfizer* requires an advertiser to possess a reasonable basis consisting of evidence that "would satisfy a reasonable and prudent businessman, acting in good faith, that such representation is true." 81 F.T.C. at 64, quoted at C.A.B. p. 64. This standard, complaint counsel contend, precludes the making of inconsistent claims because, having made a claim for one product, no advertiser could reasonably make an inconsistent claim for a competing product which it also sold to the public. Reasonableness, complaint counsel argue, cannot be judged solely in terms of the quantity of evidence supporting a given claim. (C.A.B. p. 65) Such conduct would be both unfair, because it places on the consumer the burden of taking the gamble as to which claim is correct, and deceptive, because the making of a claim implies the existence of a reasonable basis.

Finally, complaint counsel argue that on numerous occasions in the past the Commission has determined that the making of mutually inconsistent claims constituted a violation of the F.T.C. Act. To support this, they cite cases such as *Rudolph R. Siebert,* 49 F.T.C. 1418 (1953); *Montgomery Ward & Co., Inc.,* 70 F.T.C. 52 (1966), *aff'd,* 379 F.2d 666 (7th Cir. 1967); and *Sears, Roebuck and Co.,* 95 F.T.C. 406 (1980), *aff'd,* 676 F.2d 3985 (9th Cir. 1982).

After carefully considering complaint counsel's arguments, we conclude that it would be inappropriate for us to find that respondent violated the F.T.C. Act merely because it made inconsistent advertising claims. We believe the inconsistent claims theory would be a new theory of advertising substantiation which would shortcut and be contrary to principles of law set forth in *Pfizer* and its progeny. Thus, for the reasons set forth below, we agree with the ALJ that paragraph 17 and that portion of paragraph 29 of the complaint that relate to inconsistent claims should be dismissed. **[51]**

Complaint counsel argue that *Pfizer* requires not only an adequate quantity of support to substantiate claims but also support of a type that would satisfy a reasonable businessman that the claim is true. Inconsistent claims, complaint counsel contend, could never be reasonably substantiated because a reasonable businessman would never believe that two inconsistent claims were both true. The reasonable businessman standard quoted by complaint counsel actually comes from *H.W. Kirchner,* 63 F.T.C. 1282, 1294, and was restated by the Commission in *Pfizer,* 81 F.T.C. at 64. After quoting the substantiation standard from *Kirchner,* the opinion in Pfizer makes it clear that the *Pfizer* "test evaluates both the reasonableness of an advertiser's

actions and the adequacy of the evidence upon which such actions were based." 81 F.T.C. at 64. Thus, the reasonable basis standard in *Pfizer* subsumes the *Kirchner* standard. Each individual advertising claim alleged in paragraph 17 could have been evaluated under the *Pfizer* standard. The performance of this analysis would have determined whether Sterling's reliance on the substantiation it possessed was reasonable. However, the reasonable basis analysis does not determine whether a claim is true. *See Pfizer,* 81 F.T.C. at 67 n. 22. Therefore, it is at least theoretically possible that two inconsistent claims could both be substantiated with a reasonable basis. In effect, the approach recommended by complaint counsel would bypass the *Pfizer* analysis in favor of a rule finding liability based solely upon the wording of advertising, regardless of the substantiation possessed by the advertiser.

The inconsistent claim theory would also produce an anomalous result described in respondent's answering brief. (R.An.B. p. 54) If an advertiser made inconsistent claims regarding products A and B, the advertiser would have automatically violated the F.T.C. Act. If, however, one advertiser made the claim regarding product A and a competing advertiser made the inconsistent claim regarding product B, the claims would be judged under a reasonable basis standard and it is possible that neither advertiser would be found to have violated the law. By applying the reasonable basis standard to all claims, regardless of the advertiser, the above result can be avoided.

Finally, we find that the previous Commission cases cited by complaint counsel do not actually apply the inconsistent claim theory proposed by complaint counsel. A good example is the *Sears* case. In that case, Sears advertised that no pre-soaking was necessary prior to washing dishes in the Lady Kenmore dishwasher. The owner's manual, however, said just the opposite. The Commission held that Sears lacked a reasonable basis for its claim and entered an order which, among other things, prohibited Sears from making any claims in its advertising that were contradicted in an owner's manual given to a consumer after purchase. Complaint counsel contend that this is an example of the inconsistent claim theory. **[52]** However, the Commission (and the ALJ) in *Sears* carefully examined the substantiation possessed by Sears and determined that it did not have a reasonable basis for its claim. 95 F.T.C. at 426–469, 514. The fact that the owner's manual contained inconsistent statements was merely a factor considered in determining whether the advertising was adequately substantiated. The analysis performed in *Sears* was not the abbreviated inconsistent claim analysis proposed by complaint counsel.

Thus, we find that the inconsistent claim theory is not appropriate for analyzing advertising substantiation. The advertising claims set

forth in paragraph 17 of the complaint could have been each individually challenged for lacking a reasonable basis under *Pfizer*. Since this was not done, we agree with the ALJ that complaint paragraph 17 and that portion of paragraph 29 relating to inconsistent claims should be dismissed.[53] **[53]**

VII. LIABILITY OF LOIS HOLLAND CALLAWAY

The complaint in this case charges the advertising agency, Lois Holland Callaway, Inc., with responsibility for certain advertising claims regarding Vanquish. We dismiss each of these charges since we have ruled that the ads in question were not deceptive.

Specifically, paragraph 8 charges the agency with falsely representing it has been established that Vanquish is more effective than aspirin and less likely to cause stomach upset than unbuffered analgesics. However, as we indicated above, (*supra* pp. 16–19) the challenged advertising contains no establishment representations regarding Vanquish. In paragraph 12, Lois Holland Callaway is charged with representing that Vanquish is a more effective pain reliever and less likely to cause stomach upset, without disclosing that a substantial question existed among experts as to the validity of these claims. For reasons explained above (*supra* p. 37), we dismissed all claims based on the substantial question theory. In paragraph 23, Lois Holland Callaway is charged with failing to disclose in advertising the presence of aspirin and caffeine in Vanquish. As we explained above (*supra* p. 45), this would constitute a violation of the FTC Act only if the advertising also represented or implied that Vanquish did not contain aspirin. We found that Vanquish advertising created no such implication. We therefore have dismissed all unfair or deceptive advertising claims with which Lois Holland Callaway has been charged.

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[53] Sterling has also raised objections to several of the ALJ's evidentiary rulings. First, it objects because the ALJ refused to admit into evidence approximately 160 scientific articles. (R.A.B. pp. 71–74) We find that this decision was an appropriate exercise of the ALJ's duty to manage a complex lawsuit. Although 160 articles were excluded, approximately 60 were accepted and the ALJ gave respondent the opportunity to select which articles would be admitted. (Tr. 11937–38, 18055) Furthermore, the ALJ permitted respondent's experts to quote from any of the articles and to read any passage into the record. (Tr. 11938)

Sterling also appealed the ALJ's exclusion of six unpublished scientific studies from the record. (R.A.B. 74–77) Two of the studies, RX 195 and 207, involve nonclinical tests submitted by Sterling to show it possessed a reasonable basis for superiority claims regarding Bayer. However, as we explained above (*supra* p. 38), because these claims were embellished with representations of establishment, only well-controlled clinical tests can constitute a reasonable basis for Bayer's superiority. Respondent was not harmed by the ALJ's rejection of RX 415 because that exhibit was submitted to support the claims of Bayer's superior quality and we held that complaint counsel failed to meet their burden of proof on that issue. RX 197 was rejected as being duplicative of other evidence on the record. The ALJ did, nonetheless, permit testimony regarding the study (*e.g.* Fields, Tr. 16758–61). There is no evidence that respondent was prejudiced by this evidentiary decision. RX 190 was rejected by the ALJ because it was unpublished, the author was reporting on a study by someone else, and Sterling called no foundation witness. Without a proper showing of reliability, rejection of RX 190 was proper. *Bristol-Myers*, 85 F.T.C. 688, 743–744 (1975). Finally, respondent was not prejudiced by the rejection of RX 422. The record shows that RX 422 was not complete (Tr. 17921–27) and, although given the opportunity to have the study's author testify (Tr. 15082), respondent chose not to call him. Nonetheless, the ALJ did admit an abstract of the complete study. (Tr. 17926–27) Thus, there was no error in the rejection of RX 422.

VIII. RELIEF

The order we enter today proscribes the violations of the FTC Act committed by respondent. It also prohibits related violations in order to assure respondent's future compliance. *F.T.C.* v. *Ruberoid Co.*, 343 U.S. 470, 473 (1952); *American Home Products*, 98 F.T.C. at 398.

However, there are differences between our order and the one entered by the ALJ. First, we dismissed those allegations of the complaint based upon the substantial question theory of advertising substantiation. The ALJ's order would have required respondent either to substantiate all comparative efficacy claims with well-controlled clinical tests, or to disclose in ads making those claims that the claims had not been proven. Our order imposes the clinical testing requirement only on those ads which claim that an analgesic's superiority has been established.

Second, the ALJ's order required that respondent possess a reasonable basis for any claim it makes regarding any nonprescription drug. We decline to enter so broad an order provision. However, since we have found instances in which respondent lacked an appropriate level of substantiation for both comparative and noncomparative therapeutic performance claims, our order requires Sterling to possess a reasonable basis for any therapeutic performance claim it makes regarding an OTC internal analgesic. [54]

The ALJ also entered an order provision imposing specific substantiation requirements for all claims regarding pharmaceutical quality. (I.D. pp. 353–354) As we discussed above, we found that complaint counsel failed to meet its burden of showing that respondent lacked adequate substantiation for its claims regarding Bayer's overall pharmaceutical quality. Accordingly, we have limited this order provision to claims regarding specific product attributes. These were the only claims related to pharmaceutical quality which complaint counsel showed respondent failed to substantiate. Additionally, our order narrows the scope of the aspirin disclosure required by the ALJ, limiting the disclosure of aspirin's presence to those ads for analgesics which contrast the advertised product with aspirin. Finally, we have limited the product coverage of some of the order provisions. Each of these modifications is discussed below.

A. *Establishment Claims.*

Paragraph I of the order sets forth the level of support which Sterling must possess before it can advertise that the superior effectiveness of any nonprescription internal analgesic product has been established. These types of claims must be supported by two well-controlled clinical studies meeting the criteria set forth in subpara-

graphs A-C of paragraph I. Testimony in this case shows that experts require studies to meet these criteria in order to establish an analgesic's superior efficacy. (*Supra* pp. 21–32) Indeed, we imposed the same testing requirement in *American Home Products* and *Bristol-Myers* based upon the expert testimony elicited in those cases. However, as in *Bristol-Myers,* slip op. at 67 [102 F.T.C. at 372], we have included paragraph I D in order to avoid penalizing Sterling for purely technical instances of noncompliance with the detailed provisions of paragraph I, if Sterling can show that the scientific community would not regard the violation as affecting the adequacy of support for the claims.

The ALJ's order applied the clinical testing requirement to establishment claims made by Sterling regarding any nonprescription internal analgesic product and we agree with this product coverage. Complaint counsel have argued that the clinical testing requirement should apply to establishment claims regarding all OTC drugs. (C.A.B. pp. 27–35) However, we rejected similar arguments in both *Bristol-Myers* and *American Home Products.* As we held in *American Home Products,* 98 F.T.C. at 402–403, it is possible that claims of superiority for other drug products may be established by other than two well-controlled clinical tests. Indeed, there is testimony in this case that nonclinical tests can establish the efficacy of antacids. (Scoville, **[55]** Tr. 14476–81) Thus, it would not be appropriate for us to apply paragraph I of the order to all OTC drugs and we, therefore, limit its applicability to OTC internal analgesics.

On the other hand, we do not believe that application of this part of the order should be limited to the specific brands involved in this case, *i.e.,* merely to Bayer and Cope. In determining the breadth of an order provision, we must consider the extent of violations the transferability of the violations to other contexts, and any past history of violations. *See Sears, Roebuck and Co.* v. *F.T.C.,* 676 F.2d 385, 391–396 (9th Cir. 1982).

Respondent's violative ads were widely disseminated over several years. For example, the advertisements representing that Bayer's therapeutic superiority had been established were disseminated more than 2,600 times over a 29–month period. Also, respondent Sterling does have a previous history of dealings with the F.T.C.[54] Finally, and

[54] In 1950, the Commission entered a litigated order against Sterling based in part upon false advertising representations made regarding Bayer Aspirin. *Sterling Drug, Inc.,* 47 F.T.C. 203 (1950). In that case the Commission entered an all products order against Sterling. 47 F.T.C. at 214. On four occasions subsequent to that litigation, Sterling has consented to the entry of cease and desist orders. 49 F.T.C. 1635 (1953) (efficacy claims regarding "Campho-Phenique"); 61 F.T.C. 1008 (1962) (false representations regarding the safety of "Isuprel," a drug for oral inhalation); 73 F.T.C. 979 (1962) (false representations regarding the efficacy of a dietary supplement, "Super Ironized Yeast"); 84 F.T.C. 547 (1974) (false claims regarding medical benefits from using the spray disinfectant, "Lysol"). We do not take these consent orders as evidence of prior guilt. However, they are relevant for determining the appropriate scope of relief. Each of those consent orders applied not only to the product which had allegedly been falsely advertised, but also to other similar products. Thus, in no instance has an order entered against Sterling been limited in its scope solely to the product which was the subject of the proceeding.

most important, it is clear that respondent could easily change the names of some of its products or make inadequately substantiated claims of established superiority regarding other OTC internal analgesics. The evidence shows that respondent made inadequately substantiated establishment claims regarding both Bayer and Cope. Although we did not find a violation, the record also shows that respondent made claims of therapeutic superiority for Vanquish. Thus, our order requires all claims of established comparative efficacy made by Sterling regarding OTC internal analgesics to be substantiated by two well-controlled clinical tests. **[56]**

In numerous previous cases the Commission has issued (and courts have upheld) cease and desist orders applying to all of a company's products based upon violations committed in the advertising of only one, or a few, products. *E.g., Litton Industries, Inc.*, 97 F.T.C. 1 (1981), *aff'd*, 676 F.2d 364 (9th Cir. 1982) (misrepresentations regarding microwave oven, order applied to any product used for personal or household purposes); *Sears, Roebuck and Co.*, 95 F.T.C. 406 (1980), *aff'd*, 676 F.2d 385 (9th Cir. 1982) (misrepresentations regarding dishwasher, order applied to 12 major home appliances); *Jay Norris Corp.*, 91 F.T.C. 751 (1978), *aff'd*, 598 F.2d 1244 (2d Cir. 1979), *cert. denied*, 444 U.S. 980 (1979) (misrepresentations regarding six products, order covered general mail order merchandise); *Porter & Dietsch, Inc.*, 90 F.T.C. 770 (1977), *aff'd*, 605 F.2d 294 (7th Cir. 1979), *cert. denied*, 445 U.S. 950 (1980) (one product was misrepresented, order covered any good, drug, cosmetic or device); and *I.T.T. Continental Baking Co.*, 83 F.T.C. 865 (1973), *modified on other grounds*, 523 F.2d 207 (2d Cir. 1976) (Wonder Bread was misrepresented, order applied to any food product). The coverage of this order provision is much more narrow, applying only to other OTC internal analgesics.[55]

Paragraph II of our order applies to establishment claims which respondent makes regarding Bayer's superior pharmaceutical quality. Complaint counsel argue that these claims must be substantiated with well-controlled clinical studies because all claims of superior pharmaceutical quality imply therapeutic superiority. (C.A.B. pp. 9–27) However, as we explained above, we do believe that consumers can understand pharmaceutical or manufacturing quality (if properly characterized) as a concept separate from therapeutic superiority. It is true that many of respondent's ads which claim that Bayer is pharmaceutically superior also impliedly represent that it is therapeutically superior. But there are other ads which make representations regarding Bayer's pharmaceutical quality only. As we discussed in the liability section, Sterling's ads claimed that its tests demon-

[55] According to material submitted by Sterling to the Physician's Desk Reference (36th ed. 1982), as of 1982 Sterling manufactured 5 OTC internal analgesics.

strated both Bayer's overall pharmaceutical superiority to other aspirin as well as its superiority in terms of four specific attributes (purity, freshness, stability and speed of disintegration). Complaint counsel failed to meet its burden of showing that the tests Sterling performed do not establish Bayer's overall [57] pharmaceutical superiority. They also failed to show what sort of evidence experts require to establish the pharmaceutical superiority of an analgesic. It is, therefore, inappropriate for us to enter any order provision detailing a specific level of substantiation which Sterling must possess when it represents that Bayer is pharmaceutically superior.

Nonetheless, even a facial examination of respondent's support for its claims shows that other brands of aspirin were at least as pure, as fresh, as stable and as quick to disintegrate as Bayer. Thus, Sterling does not possess support demonstrating or establishing Bayer's superiority with respect to those attributes. Paragraph Part II of our order accordingly requires that when respondent represents that it has been established that an OTC internal analgesic is fresher, purer, more stable, or quicker to disintegrate than others, it must possess support for that claim which would satisfy relevant experts that the product has the superiority attributed to it. However, at this time we reach no conclusion as to what type or what quantity of evidence is necessary to satisfy that burden.

B. *Reasonable Basis Provision.*

Paragraph III of our order requires Sterling to possess a reasonable basis for all therapeutic performance claims regarding OTC internal analgesics. As a practical matter, this paragraph applies primarily to those claims that are not presented (either expressly or implicitly) as claims whose truth has been scientifically established. For establishment claims, Sterling will be held to the more specific standards set forth in Paragraph I, so Paragraph III adds nothing to Sterling's obligations with respect to establishment claims. The purpose of Paragraph III is to hold Sterling to a more general reasonable basis standard for all other "non-establishment" claims.

A similar provision was entered in our order against Bristol-Myers (slip op. at pp. 70–73) [102 F.T.C. at 374–377], and our reasons for entering one here are very similar. While we are unwilling to go as far as the ALJ's order, which would have imposed a reasonable basis requirement for all claims for all nonprescription drugs, we believe that a requirement limited to therapeutic performance claims for OTC analgesics is reasonably related to the violations found. Most of the claims in the case were establishment claims and we found that Sterling did not possess adequate substantiation for any of those claims. Our concern is that this violation, the making of inadequately

substantiated claims, can easily be transferred to other sorts of claims, including non-establishment claims. [58]

Moreover, in this case the record shows that respondent has already made a number of non-establishment claims without possessing the evidence required to satisfy the reasonable basis standard. We found ten such violations in its tension relief advertisements for Cope, and another 16 violations in similar advertisements for Midol (*supra* at p. 39). As we noted in *Bristol-Myers,* such a record (combined with the other factors dismissed in the previous section, such as the history of prior violations) might well justify an order extending to all claims or to all nonprescription products. Instead, we are limiting this provision to therapeutic performance claims for OTC analgesics—*i.e.,* to the exact product category and claims involved in this case. Paragraph III, thus, has a much closer relation to the violations involved here than did the broader reasonable basis provision that was struck down on appeal in *American Home Products* v. *FTC,* 695 F.2d at 710–711.

Finally, we note that paragraph III specifies that two well-controlled clinical tests will always be sufficient to constitute a reasonable basis, but it also permits Sterling to satisfy this requirement with any other "competent and reliable evidence" sufficient to provide a reasonable basis for the challenged claim. While this more general standard does leave some ambiguity regarding the absolute minimum level of evidence required to satisfy paragraph III, some flexibility is inherent in any reasonable basis order. For the reasons already discussed at length in our *Bristol-Myers* opinion (slip op. pp. 71–73) [102 F.T.C. at 375–377], we believe that the flexibility provided by paragraph III represents an appropriate balance between the need for clear standards and the need to prevent repeated violations. Should Sterling ever be in doubt about the level of evidence required for any further claim, it can always: (a) take advantage of paragraph III's "safe harbor" by conducting two well-controlled clinical tests; (b) request an advisory opinion from the commission pursuant to Rule 2.41; or (c) qualify its advertising claim to make consumers aware of the lower level of substantiation.

C. *Ingredient Claims and Omissions.*

Sterling's advertisements falsely represented that the pain reliever in Midol was special or unique and that Cope was the only OTC analgesic containing both a pain reliever and a sedative. (*supra* pp. 45–49) Under paragraph IV of the order, Sterling may not represent that a product contains any special, unusual or unique ingredient or ingredients when the same ingredients are used in other nonprescription drug products intended for the same purpose. This is the only provision of our order which we believe should apply not only to

claims regarding analgesics but to advertising claims made by respondent regarding any nonprescription drug. In determining the scope of this provision, we have considered [59] the same factors discussed in connection with paragraphs I and II of the order. First and foremost, as we discussed in *Bristol-Myers,* a false claim regarding ingredients could be made for any drug product. Second, documents from Sterling's files show it was fully aware that Cope's ingredients were not unique and that another analgesic on the market, Excedrin P.M., contained both a pain reliever and a sedative. Third, as we discussed above, this is the second time a cease and desist order has been entered against Sterling regarding the advertising of its OTC analgesics. These reasons justify entry of a broad order provision applying to all nonprescription drugs advertised by Sterling.[56]

In its appeal brief, respondent argues that entry of any order provision applying to all drugs is unjustified because there is no showing that Sterling has a history of past violations. In addition, Sterling assures us that its advertising claims were all made in good faith. (R.A.B. pp. 77–80) However, in determining the appropriate scope of order provisions, we consider all the factors discussed in *Sears.* Taken in conjunction, the ease with which the violation could be transferred to other drugs, Sterling's past history of violative advertising, and the fact that it appears Sterling knew its Cope ads were false all justify entry of an order applying to all drugs.

The purpose of paragraph V is to prevent respondent from passing off its aspirin-based analgesic products as being different from aspirin or from otherwise misrepresenting the identity of any analgesic ingredient. The principal means by which this deception has been accomplished in the past, has been to create the impression that some analgesic ingredient in respondent's product is different from the ingredient in any competing analgesic. To prevent this practice, paragraph V prohibits any misrepresentation that the analgesic ingredient in an aspirin-containing product is different from aspirin. To prevent closely related violations, the order prohibits misrepresentations regarding the identity of any analgesic ingredient in respondent's products. The order also makes clear that any attempt to contrast with aspirin the ingredient in an aspirin-based analgesic without disclosing that the ingredient in respondent's product is also aspirin, will violate the order.

The ALJ's order would have required the disclosure of aspirin's presence in any ad for an aspirin-based analgesic. However, nondisclosure of aspirin constitutes a violation only in those instances in which respondent falsely represents that the advertised product does

[56] According to material submitted by Sterling to the *Physician's Desk Reference for Nonprescription Drugs* (1st ed. 1980) as of 1980, Sterling manufactured 36 nonprescription drug products.

not contain aspirin. Thus, paragraph V is specifically tailored to prevent the sort of violation committed by respondent. **[60]**

D. *Labeling*

The order entered by the ALJ in this case applied not only to respondent's advertising, but also to the labeling of its products. As we stated in both *American Home Products,* 98 F.T.C. at 411, and *Bristol-Myers,* slip op. at p. 76 [102 F.T.C. at 380], our liaison agreement with the FDA recognizes that primary responsibility for labeling of nonprescription drugs rests with that agency. For the reasons we set forth in *American Home Products,* the order which we enter does not apply to labeling.

E. *Corrective Advertising.*

In their appeal brief, complaint counsel request that we impose a corrective advertising requirement on Sterling and require it to include a notice in its advertising disclosing that Bayer has not been proven therapeutically superior to other aspirin. (C.A.B. pp. 37–60) The ALJ declined to require corrective advertising and we agree that it would not be appropriate in this case.

Corrective advertising is a remedy available to the Commission. *Warner-Lambert Co.* v. *F.T.C.,* 562 F.2d 749, 756–759 (D.C. Cir. 1977), *cert. denied,* 435 U.S. 950 (1978). Two inquiries must be made in order to determine if it is appropriate: (1) Did the advertisements in question play a substantial role in creating or reinforcing a false belief in the public's mind regarding the product; and (2) Will the belief remain after the advertising ceases? *Warner-Lambert Co.* v. *F.T.C., Id.* at 762. Based upon our analysis of the evidence in this case, we agree with the ALJ that it is not clear that respondent's advertising played a substantial role in creating or reinforcing a false belief regarding Bayer in the public's mind.

The record contains the results of several surveys which attempted to assess the public's image of Bayer. (F. 1240–1310). Two of these surveys are particularly significant. The first is the Assets and Liabilities Study, CX 395, which measured consumer attitudes regarding Bayer in 1967, prior to the dissemination of any of the ads which are the subject of this case. The other is the Zeisel Image Study, CX 521 which was conducted in 1975, after the dissemination of challenged ads. Although a comparison of the results of these two studies is apparently somewhat difficult to perform, complaint counsel concede that the results show that Bayer's image remained relatively stable throughout the eight-year period between the two studies. (C.A.B. p. 51) Based upon this, it is difficult to conclude that Sterling's advertising created or reinforced **[61]** the public's belief regarding Bayer's

superiority. Complaint counsel argue that even though the public's image of Bayer may have remained stable during the period, it nonetheless became "sharper," that is, more of those surveyed in 1975 had opinions than in 1967. To support this they cite the testimony of Dr. Brock, an expert, in the analysis of image studies. (Tr. 5155–59) Respondent countered Dr. Brock's testimony with the testimony of its own expert, Dr. Amstutz (Tr. 10164–90). We find this evidence regarding "sharpness" inconclusive and do not believe that it supports imposition of corrective advertising.

Complaint counsel also argue that the need for corrective advertising may be inferred directly from the advertising. We decline to draw such an inference in this case. Although the ads representing Bayer's comparative superiority were disseminated on several thousand occasions, we do not think that in this case that is adequate to justify corrective advertising. Indeed, the violative ads represent only a portion of the Bayer ads which appeared during the early 1970's. (The record contains nearly twice as many Bayer ads which did not represent its therapeutic superiority.) In light of survey evidence which appears to indicate no need for corrective advertising, we find such a need may not be inferred directly from the ads.

Numerous factors contribute to a product's image. Included among these are consumers' experience with the product, publicity regarding the product, longevity and visibility in the market, amount of advertising (regardless of content), advertising content and other sources. (Miles, Tr. 9355–59) The longer a brand has been in existence, the less its image stems from one particular advertising campaign. (Miles, Tr. 9366) For a brand such as Bayer, which has been on the market for many years, familiarity is the primary influence on brand image. (Haley, Tr. 10569) Complaint counsel contend that this case is similar to *Warner-Lambert* in which the Commission ordered corrective advertising regarding Listerine, a well-established brand. (C.A.B. p. 42) However, in *Warner-Lambert,* the record showed that the respondent had been making false claims regarding Listerine in its advertising for more than 50 years and that throughout that period the false claim had been a major theme of the advertising, 86 F.T.C. 1398, 1501. The corrective advertising was designed to correct that false advertising. In this case, there has been no showing that the false advertising was so extensive. Sterling's false advertising was disseminated during only a 29–month period, and the public's image of Bayer remained stable during that period. Thus, since it has not been shown that Sterling's advertising created or reinforced the public's image of Bayer, corrective advertising is an inappropriate remedy.

X. CONCLUSION

For the reasons set forth above, the initial decision of the administrative law judge is modified as described. An appropriate order is appended.

SEPARATE STATEMENT OF COMMISSIONER PERTSCHUK CONCURRING IN PART AND DISSENTING IN PART*

For the reasons stated in my separate opinion in *Bristol-Myers* (D. 8917) [102 F.T.C. at 382], announced today, I dissent from that portion of the Commission's opinion which reverses the "substantial question" doctrine developed in *American Home Products,* 98 F.T.C. 136 (1981), *aff'd,* 695 F.2d 681 (3d Cir. 1982). Therefore, I dissent from the Commission's decision to dismiss paragraphs 12 through 14 of the complaint.

I also dissent from the portion of the Commission's opinion which dismisses complaint paragraphs 17 and 29, which allege that Sterling violated Section 5 by making contemporaneous inconsistent claims for its OTC internal analgesic drug products. The Commission dismisses these charges, not because Sterling did not make such claims, but because it sees the basis of the charge as a "new theory of advertising substantiation which would shortcut and be contrary to principles of law set forth in *Pfizer* and its progeny." Slip op. at 50. [102 F.T.C. at 358]

I disagree. The inconsistent contemporaneous claims allegation stems directly from the reasonable basis doctrine set out in *Pfizer.* In my view, application of the reasonable basis doctrine to an examination of the claims made by Sterling in this case leads inexorably to the conclusion that Sterling has made unsubstantiated claims in violation of Section 5.

The Commission agrees that Sterling represented that Vanquish was better than aspirin in relieving pain and in avoiding stomach upset (slip op. at 16, 18) [102 F.T.C. at 329, 331], and that Cope was superior to any OTC analgesic for the relief of nervous tension headache (slip op. at 20) [102 F.T.C. at 332]. At the same time it was making those claims, however, Sterling was *also* claiming that Bayer aspirin was just as good as *any* internal analgesic in relieving pain and nervous tension headaches, and avoiding stomach upset. (F. 398–402)

There is simply no way those statements can be reconciled. Sterling's claims that Vanquish and Cope were more effective than aspirin plainly conflict with Sterling's contemporaneous claim that Bayer

* Statements by Chairman Miller and Commissioners Bailey and Douglas concerning this order were issued with the Final Order in *Bristol Meyers Co., et al. See* 102 F.T.C. 381, 386, 389.

aspirin was just as effective as any OTC internal analgesic—presumably, including Vanquish and Cope. Both statements can not be true at the same time.

Nevertheless, the Commission declines to find a violation on the ground that a reasonable basis analysis does not determine whether a claim is true, and that therefore it is "theoretically possible that two inconsistent claims can both be substantiated with a reasonable basis." Slip op. at 51. [102 F.T.C. at 358] [2]

While it might be theoretically possible for two inconsistent claims to be adequately substantiated, the problem with the Commission's rationale is that it fails to consider whether it is even theoretically possible for each claim made by Sterling in *this case* to be adequately substantiated. It appears obvious to me that they cannot. If Sterling has a reasonable basis for a claim that Vanquish provides superior pain relief to aspirin, it cannot have a reasonable basis for a claim that Bayer aspirin relieves pain just as well as all OTC internal analgesics. Conversely, if Sterling has a reasonable basis for a claim that aspirin relieves pain just as effectively as all OTC internal analgesics, it cannot have a reasonable basis for a claim that Vanquish relieves pain better than aspirin. Where an advertiser makes an objective and verifiable claim that its product performs better than *any* other product, adequate substantiation for that claim necessarily precludes the advertiser from having a reasonable basis for a claim that another product works better than, or as well as, the one advertised.

The Commission seems troubled, however, by the application of an "inconsistent contemporaneous claims" theory. It notes the apparent discrepancy between the case where a single advertiser is held liable for making inconsistent claims, and the case where the same claims are made separately by two different advertisers and the Commission finds each adequately substantiated. In fact, such a result would not be anomalous. Indeed, it would be perfectly consistent with the reasonable basis doctrine, which takes into account not only the sufficiency of the evidence on which an advertiser relies but also "the reasonableness of the advertiser's action and his good faith." *National Dynamics Corp.*, 82 F.T.C. 488, 553 (1973). In considering an advertiser's reasonableness, the Commission routinely considers information in the advertiser's possession which might give the advertiser reason to question the evidence relied upon to substantiate a claim. Clearly, an advertiser possessing data which directly contradicts a claim cannot have a reasonable belief in the truth of that claim. On the other hand, if the contradictory evidence exists but the advertiser is unaware of it and would have no reason to know about it, the advertiser would not be precluded from making the claim. In other words,

whether or not there is liability depends, at least in part, on the advertiser's knowledge. The application of the inconsistent contemporaneous claims theory simply is one example of the effect of this standard, and accordingly reflects no deviation from the established reasonable basis doctrine.

It is true, as the majority notes, that we could have proceeded to determine *which* of Sterling's claims was the one that lacked a reasonable basis. But where the conclusion is inescapable, as it is here, that one claim or the other lacked a reasonable basis, it seems like a waste of resources to require both sides to go through the full panoply of evidentiary exchanges just to find out which claim was the one to violate [3] Section 5. Accordingly, I would have sustained the allegations of the complaint with respect to the making of contemporaneous inconsistent claims.

FINAL ORDER

The matter has been heard by the Commission upon the appeal of counsel for respondent Sterling Drug, Inc., and complaint counsel and upon briefs and oral argument in support of and in opposition to the appeals. The Commission, for reasons stated in the accompanying Opinion, has granted a portion of respondent's appeal and denied that of complaint counsel. Therefore

It is ordered, That the initial decision of the administrative law judge be adopted as the Findings of Fact and Conclusions of Law of the Commission except as is otherwise inconsistent with the attached opinion.

Other Findings of Fact and Conclusions of Law of the Commission are contained in the accompanying Opinion.

It is further ordered, That the following Order to Cease and Desist be entered. [2]

ORDER

I

It is ordered, That Sterling Drug, Inc., its successors and assigns, and its officers, agents, representatives and employees, directly or through any corporation, subsidiary, division or other device, in connection with the advertising, offering for sale, sale or distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol," or other nonprescription internal analgesic product, in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from:

Making any representation, directly or by implication, that a claim concerning the superior effectiveness of such product has been established or proven unless such representation has been established by two or more adequate and well-controlled clinical investigations, conducted by independent experts qualified by training and experience to evaluate the comparative effectiveness of the drugs involved, on the basis of which it could fairly and responsibly be concluded by such experts (1) that the drug will have the comparative effectiveness that it is represented to have, and (2) that such comparative effectiveness is demonstrated by methods of statistical analysis, and with levels of confidence, that are generally recognized by such experts. The investigations shall be conducted in accordance with the procedures set forth below.

At least one of the adequate and well-controlled clinical investigations to evaluate the comparative effectiveness of the drug shall be conducted on any disease or condition referred to, directly or by implication, or, if no specific disease or condition is referred to, then the adequate and well-controlled clinical investigations shall be conducted on at least two conditions or diseases for which the drug is effective. The clinical investigations shall be conducted as follows:

A. The subjects must be selected by a method that:

1. Provides adequate assurance that they are suitable for the purposes of the investigation, and the diagnostic criteria of the condition to be treated (if any); [3]

2. Assigns the subjects to the test groups in such a way as to minimize bias; and

3. Assures comparability in test and control groups of pertinent variables, such as age, sex, severity or duration of disease or condition (if any), and use of drugs other than test drugs.

B. The investigations must be conducted double-blind, and methods of double-blinding must be documented. In addition, the investigations shall contain a placebo control to permit comparison of the results of use of the test drugs with an inactive preparation designed to resemble the test drugs as far as possible.

C. The plan or protocol for the investigations and the report of the results shall include the following:

1. A clear statement of the objective of the investigation;

2. An explanation of the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subject's response and steps taken to minimize bias on the part of the subject and observer;

3. A comparison of the results of treatments or diagnosis with a

control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data;

4. A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

D. A test or investigation which is not conducted in accordance with these procedures may be used to establish a claim only if respondent can show that, notwithstanding the failure to satisfy these procedures, the test or investigation would still be generally accepted by the relevant scientific community as sufficient to establish the truth of the claim. [4]

II

It is further ordered, That respondent Sterling Drug, Inc., a corporation, its successors and assigns, and its officers, agents, representatives and employees, directly or through any corporation, subsidiary, division or other device, in connection with the advertising, offering for sale, sale or distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol," or any other nonprescription internal analgesic product, in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from making any representation, directly or by implication, that the superior freshness, purity, stability, or speed of disintegration of such product has been established, demonstrated, or proven unless at the time such representation is made, respondent possesses and relies upon competent and reliable scientific evidence which would permit qualified experts to conclude that the product has the comparative pharmaceutical qualities it is represented to have.

III

It is further ordered, That respondent Sterling Drug, Inc., its successors and assigns, and its officers, agents, representatives and employees, directly or through any corporation, subsidiary, division or other device, in connection with the advertising, offering for sale, sale or distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol" or any other nonprescription internal analgesic, in or affecting Commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from making any therapeutic performance claim for such product unless respondent possesses a reasonable basis for making that claim. A

reasonable basis for such a claim shall consist of competent and reliable scientific evidence supporting that claim. Well-controlled clinical tests conducted in accordance with the criteria set forth in Order Paragraph I shall be deemed to constitute a reasonable basis for a claim.

IV

It is further ordered, That respondent Sterling Drug, Inc., its successors and assigns, and its officers, agents, representatives and employees, directly or through any corporation, subsidiary, division or other device, in connection with the advertising, offering for sale, sale or distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol," or any other nonprescription drug product in or affecting commerce, as "commerce" and "drug" are defined in the Federal Trade Commission Act, do forthwith cease and desist from making any representation, [5] directly or by implication that such product contains any unusual, special or unique ingredient or ingredients when such ingredient or ingredients are commonly used in other nonprescription drug products intended for the same use or uses as the product advertised by respondent.

V

It is further ordered, That respondent Sterling Drug, Inc., its successors and assigns, and its officers, agents, representatives and employees, directly or through any corporation, subsidiary, division or other device, in connection with the advertising, offering for sale, sale or distribution of "Bayer Aspirin," "Bayer Children's Aspirin," "Vanquish," "Cope," "Midol," or any other nonprescription internal analgesic in or affecting commerce, as "commerce" is defined in the Federal Trade Commission Act, do forthwith cease and desist from falsely representing that the analgesic ingredient in an aspirin-containing product is different from aspirin or otherwise misrepresenting the identity of any analgesic ingredient. It shall be a violation of this paragraph to contrast the analgesic ingredient of a product which contains aspirin with the analgesic ingredient of another product if that product also contains aspirin, unless respondent discloses clearly and conspicuously that the analgesic ingredient in its product is aspirin.

VI

It is further ordered, That respondent Sterling Drug, Inc., shall notify the Commission at least thirty (30) days prior to any proposed change in the corporation such as a dissolution, assignment or sale resulting in the emergence of a successor corporation, the creation or dissolution of subsidiaries or any other change in its corporation which may affect compliance obligations under this Order.

VII

It is further ordered, That the respondent herein shall within sixty (60) days after service of this Order upon it and at such other times as the Commission may require, file with the Commission a written report setting forth in detail the manner and form in which it has complied or intends to comply with this Order. [6]

Complaint paragraphs Eight A.2, Eight B, Eight C, Ten B, Twelve, Thirteen, Fourteen, Fifteen A, Seventeen, Twenty-Three, Twenty-Four, and that portion of Twenty-Nine which refers to Seventeen are hereby dismissed.

IN THE MATTER OF

THE MAGNAVOX COMPANY

MODIFYING ORDER, ETC., IN REGARD TO ALLEGED VIOLATION OF SEC. 5 OF THE FEDERAL TRADE COMMISSION ACT

Docket 8822. Consent Order, June 9, 1971—Modifying Order, July 11, 1983

This order reopens the proceeding and modifies the Commission's order issued on June 9, 1971 (78 F.T.C. 1183), by amending Part I-T and deleting Part I-V of the order, to permit the company to control the transshipment of its consumer electronic products. The modification also deletes Part III of the order, which had prohibited the company from engaging in exclusive dealing, full line forcing and tying practices in connection with the sale of its products.

ORDER MODIFYING DECISION AND ORDER

On February 2, 1983, respondent The Magnavox Company ("Magnavox") filed its "Request To Reopen And Modify Consent Order" ("Request"), pursuant to Section 5(b) of the Federal Trade Commission Act, 15 U.S.C. 45(b), and Section 2.51 of the Commission's Rules of Practice. The Request asked that the Commission reopen the consent order that was issued on June 9, 1971, in this matter ("the order") and modify it in two respects. First, Magnavox requested that certain words in Part I-T of the order and all of Part I-V be deleted to eliminate order language that prevents Magnavox from prohibiting transshipment of its consumer electronic products. Second, Magnavox requested that the Commission delete Part III of the order, which forbids respondent from engaging in exclusive dealing, full line forcing and tying practices in connection with the sale and distribution of its consumer electronic products. Magnavox's Request was on the public record for thirty days and no comments were received.

After reviewing respondent's Request, the Commission has concluded that the public interest warrants reopening and modification of the order in the manner requested by respondent.

The transshipment provisions of the order were adopted as "fencing-in" restraints ancillary to the order's ban on resale price maintenance. *See FTC v. National Lead Co.*, 352 U.S. 419 (1957). Respondent has specifically represented in its Request that it does not fix the price at which its customers resell any of the products purchased from it, that prices vary from outlet to outlet, and that current market conditions would prevent it from fixing resale prices even if it were so inclined. Respondent also has argued that the image of the Magnavox brand is being harmed by its inability to control transshipment of its