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,