

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 produced 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 pharmaceutical 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 salicylate 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 Acids," *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 1971-1974 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, toiletries, 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 of 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-

