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-