Review Article

Theme: Pharmacokinetics, Biopharmaceutics and Bioequivalence:
History and Perspectives
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A History of Biopharmaceutics in the Food and Drug Administration 1968–1993

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Abstract. The history of biopharmaceutics is reviewed, beginning with its origin out of the Division of Clinical Research in The Bureau of Medicine. The reason for the creation of the Division of Biopharmaceutics, the certification of Food and Drug Administration authority over the functions it was to have, and the implementation of that authority are described. The determination of bioequivalence, the bioavailability decision rules, pharmacokinetics, and drug metabolism are explained. The reason for the development of the Scale-Up and Post Approval Regulations and how they were developed are also explained.

KEY WORDS: bioavailability; bioequivalence; biopharmaceutics; FDA; pharmacokinetics; SUPAC.

CERTIFICATION OF FDA AUTHORITY

The sulfonamides were introduced in the 1930s as the first truly effective treatment for infectious disease. Because they were insoluble in aqueous fluids, parents had to crush the tablets before dosing their young children. One company solved this problem by introducing a soluble dosage form, an “elixir of sulfanilamide.” Prior to 1938, one could introduce a drug product without any toxicity testing or demonstration of effectiveness. While the elixir of sulfanilamide (solubilized by ethylene glycol, a component of antifreeze) facilitated the dosing of children, it poisoned them. When I joined FDA, I reviewed the files containing letters written to President Roosevelt by grieving parents, who upon their doctor’s orders unwittingly slowly poisoned their own children. The angst expressed in those letters was very moving. Following the deaths of those 107 children in September and October of 1937 (1), the government in 1938 enacted amendments to the Food, Drug and Cosmetic Act of 1906 requiring toxicity testing prior to the introduction of any medicinal into the marketplace.

The Food and Drug Administration (FDA) medical officer’s reviews of the first few New Drug Applications to be filed under the provisions of the new law were on the order of “The drug was administered to 12 rats: (6 male/6 female). After three days no toxicity was observed. Looks OK to me! JPS”. Both the application and medical officer’s review took up less than a single page. As time passed, the toxicology requirements became considerably more stringent. By 1962, the requirements included chronic as well as

acute toxicity testing. Also testing in several species was required. Nevertheless, efficacy data were neither required nor submitted until the October 10, 1962 amendment required it.

Thomas Rice, an FDA Inspector in Cincinnati, notified FDA headquarters in Washington DC of overt manipulation of an investigation of Mer-29, which was being studied as a cholesterol-lowering agent (personal communication from Sam Fine, FDA Associate Commissioner for Compliance). An inspectional task force from Washington appeared at the company the next day and verified Rice’s information. Francis Kelsey, M.D., Ph.D., already concerned with the same company’s failure to submit adequate toxicity data for Kevadon (thalidomide), a drug then being widely marketed in Europe, was part of that investigative team. Although under great pressure to approve thalidomide, she resisted. Eventually, it became evident that phocomelia was associated with the dosing of thalidomide to pregnant women. Nevertheless, Merrell had distributed over 2,000,000 tablets (2) for investigational use, which the Agency quickly removed from the market. For her effort, President Kennedy awarded Dr. Kelsey the “Presidents Distinguished Federal Civilian Service Award” (highest award given to a civil servant) (3). Senator Estes Kefauver’s (Tennessee) investigation of these events led to the October 10, 1962 FD&C Act amendment (the so-called Kefauver–Harris Amendments) requiring in addition to toxicological data evidence of efficacy to be submitted to the FDA, before a new drug could be marketed.

FDA interpreted the new law to mean that drugs marketed prior to the 1938 law were grandfathered and did not require FDA approval. However they also interpreted the new law as requiring efficacy data for drugs marketed between 1938 and 1962 (4). To sort things out they contracted the National Academy of Science (NAS) and National Research Council (NRC) to review the medical literature to

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determine the efficacy evidence then available. Several categories were established:

- Effective
- Probably effective
- Possibly effective
- Ineffective

Some drugs fell into more than one category, because their labeling included more than one indication. In such cases, it could be effective for one indication, but only possibly effective for another (1). Where insufficient data were available to make a determination of efficacy, time was allocated for a company to collect such data. In each case, a determination of bioavailability (to provide assurance that the dosage form then in the marketplace was indeed being absorbed into the body) was also required. More than 1,000 drugs were determined “not to be efficacious” and were removed from the market (1).

Following the 1938 amendment, both new and generic drugs were required to submit toxicity data, but given the lack of resources to review the submitted applications, FDA began to issue “Not New Drug” letters to the generic manufacturers. This meant they could market without having to submit data for FDA approval. Given the 1962 amendment and academic concern that the different formulations of all generics were not equivalent, FDA interpreted the new provisions of the act to mean that all generic drug formulations marketed between 1938 and 1962 had to file New Drug Applications (NDAs) and establish equivalency to the approved marketed brand.

While one segment of the pharmaceutical industry looked with favor on this approach, another segment viewed the FDA’s action less favorably and went to court to prevent implementation. Eventually, the courts ruled in FDA’s favor concerning the innovative section of the industry. The situation in the generic section of the industry was considerably more complicated. Congress, not anticipating the developing situation, had not enacted any legislation permitting the filing of generic drug applications. The FDA, having withdrawn the “Not New Drug” letters, established an “Abbreviated New Drug Application” (ANDA) system (1), which required FDA approval before a generic drug product could be legally marketed. Under this system, neither toxicological nor clinical studies would be required on the drug, inasmuch as FDA already had that information in the innovators’ new drug application. Essentially, the ANDA required the filing and FDA approval of Chemical Manufacturing Controls (CMC) data and a demonstration of bioequivalence to the innovative (i.e., NDA) marketed product.

This led to several problems. Some in the innovative section of the industry were incensed that FDA would use their data to approve competitive products and lobbied to force the generic industry to perform full clinical and toxicological studies. On the other hand the generic industry argued that no law existed that would require them to file any information with the agency. This latter group felt that they only had to meet United States Pharmacopeia (USP) criteria in order to market their product (5,6). The courts ruled in favor of the FDA position in regard to the use of toxicology and clinical data, but two Federal Circuit Courts (Florida and

New York) ruled in favor of the position put forward by the generic drug companies. Nevertheless, Federal Marshals at the request of FDA were intercepting shipments of these generic drug products from New Jersey to Florida, inasmuch as Florida had enacted a state law permitting the marketing of these generics in Florida. This resulted in another lawsuit in New Jersey, where the Federal Circuit Court disagreed with the Florida and New York Circuits requiring, thereby, review by the US Supreme Court.

The Supreme Court ruled that although Congress had not enacted permitting legislation, it was in the interest of the American people that FDA assure the equivalency of generic drug products. FDA, which had published proposed regulations for both innovator and generic drug products in 1972 and again in 1975 (7), then published them in final form. They became effective on July 7, 1977 (8).

While the issue was being pursued through the courts, Senator Ted Kennedy (Massachusetts) became interested in the issue. Congress had some time previously established the “Office of Technology Assessment” (OTA), but had never activated it. Senator Kennedy appointed a former New England congressman to head the office and began an immediate inquiry of the USP/FDA regulatory struggle, especially whether bioavailability testing of generic products was essential or whether meeting USP criteria was sufficient. OTA convened a panel of ten senior medical consultants, including two pharmacy professors, Dr. Sidney Riegelman (Chairman of the Department of Pharmacy at UCSF) and Dr. James Doluisio (Dean, College of Pharmacy, University of Texas): The other eight members were clinicians. After a series of meetings in which the FDA and USP and others presented data, the panel (in which Senator Kennedy was very active) formulated 11 “conclusions”. Among these, four were critical (9):

- Current standards and regulatory practices do not assure bioequivalence.
- Variations in bioavailability are recognized as responsible for a few therapeutic failures.
- Present compendia standards and GMP guidelines do not insure quality and uniform bioavailability not only for different manufacturers but also among batches produced by the same manufacturer.
- Additional research to improve bioequivalence assessment is needed.

IMPLEMENTATION OF THE LAW BY FDA

Implementation of the research and review program within the Agency proved to be as tortuous as the certification of its legal authority through the courts. FDA’s Associate and Deputy Associate Commissioners of Medicine were charged with the responsibility of writing FDA’s regulations and providing research and review resources. However resources were hard to come by in the late 1960s and early 1970s (10). With the cost of the Vietnam War increasing daily, the president, pressuring his cabinet secretaries to cut administrative costs, froze both civil service employee hiring and pay. This turned out to be a major

handicap in the implementation of the generic drug program, which was intended to reduce the cost of drugs in federal (i.e., civilian and military) institutions. The budget and personnel hiring freezes meant that personnel to be assigned to the review process had to be re-assigned from other areas, where programs were being phased out.

In 1971, Dr. Trieste Vitti was hired from the Upjohn Company to establish the program in the Division of Clinical Research of the Bureau of Medicine. He had a newly established Review Branch staffed by five scientists, placed in this assignment when their previous units were downsized. All lacked training in chemical analysis and pharmacokinetics, both requirements for this job. His Laboratory Research Branch was staffed by three technicians; none had a college degree. He resigned in frustration! I was transferred into the division and based on my credentials made "Acting Director", the intention being to develop staff. However, personnel and salary freezes delayed hiring for an additional 2 years, during which I established a review process and initiated much-needed research via FDA's extramural research program.

Although in 1969 Professor John Wagner demonstrated to the Bureau of Medicine, methods for comparing *areas under the serum versus time curve* (AUC) to estimate bioequivalence, his approach was ignored inasmuch as the FDA hierarchy did not believe a problem existed, and therefore such studies would not be necessary. For their part the Offices of Pharmaceutical Research and Compliance in the Bureau of Medicine and the Commissioner's Office believed that the "Bioavailability Problem" as some called it was a "Content Uniformity Problem" (11). In 1971 for example, when notified of a "Bioavailability Problem" with a generic digoxin product, FDA investigated and ascertained that one manufacturer first added all the excipients into a 55-gal drum, then added digoxin, closed the lid, and mixed it by rolling the drum across the floor a few times. The content uniformity of those tablets varied from 10% to 156%.

With the rapid changes taking place in the US health community, especially the need to lower drug therapy costs in Federal hospitals (civilian and military), the FDA in 1974 was reorganized to address these issues. In the process the Bureau of Medicine was reorganized into the Bureau of Drugs, in which an "Office of Drug Monographs" was established. The intended purpose for the formation of this office was for FDA to publish the formulations of various drug products, which generics could use to manufacture their product, bioequivalence being assured since the formulations would be identical. No *in vivo* bioequivalence studies would be required! However, immediately after becoming "Acting Director" of the Division of Clinical Research, I received incomplete data showing a *probable* problem with the "bioavailability" of generic digoxin products manufactured by several firms (12). Professor John Wagner, who at that time was conducting studies on digoxin under contract to the FDA, discovered a bioavailability problem with a different brand (13). Since there had been previous reports of similar problems with tetracycline (14), chloramphenicol (15), and oxytetracycline (16), I argued that FDA had a serious problem. The Commissioner's Office on the other hand felt we had evidence of bioavailability problems for only a "hand full"

of drug products. To ascertain the extent of the problem, they funded my research projects. The results of that research established that the problem was greater than they anticipated, but smaller than I had feared. Consequently, the proposed publication of drug monographs for the purpose of having bioequivalent generic drug products in the marketplace was discarded.

The decision left FDA the challenge of determining which generic drug products would require *in vivo* bioequivalence testing. I was appointed chair of a "Bureau of Drugs Bioavailability Committee", composed primarily of physicians, which had the assignment of determining, which drugs required *in vivo* studies. The physicians in the Bureau, mistrusting this new science, made their decision primarily on the basis of medical concern and only loosely on the basis of biopharmaceutic criteria. As drugs were determined to be effective, they were reviewed, the *in vivo* bioequivalence requirement was determined, and the requirement was published in the Federal Register.

DETERMINATION OF BIOEQUIVALENCE

Early in 1970, serum had been collected during an FDA-contracted bioavailability study from volunteers for the purpose of determining drug bioequivalence. Five different drugs were investigated, but equivalence/inequivalence was never determined as the methodology did not then exist to analyze the blood samples. As a result many of the generic as well as innovator companies requested waiver of the required BA studies on the basis that analytical methodology did not exist so as to permit them to do the study. To address this problem, we contracted Schools of Pharmacy to conduct a review of the literature to determine whether the analytical methodology existed for performing *in vivo* bioequivalence studies. The results were discouraging in that the required analytical methodology was largely non-existent. We then let contracts for methodology development, mostly to academic institutions, which could then be employed for the conduct of these studies.

Additionally, a Biopharmaceutics Laboratory was established under Dr. VK Prasad, which not only developed methodology for the conduct of these studies, but conducted surveys of marketed generic dosage forms. Following procedures developed under Professor Wagner's contract, samples of innovator and generic dosage forms (e.g., digoxin 0.25 and 0.5 mg) were picked up by FDA Field Inspectors and analyzed by Dr. Prasad's laboratory and FDA's National Center for Drug Analysis (NCDA) in St. Louis. Those with varying dissolution results were tested in small panels of human subjects. Where possible, *in vivo/in vitro* correlations were developed. These would eventually be used to establish dissolution specifications for the product so as to provide lot-to-lot bioequivalence assurance, once the bioequivalence to the innovator's product had been established.

Because methodology development for topical products proved to be especially difficult, a number (where one could observe clinical efficacy) were allowed to be marketed with "deferral" of the bioequivalence requirement. The thought was that when methodology was developed, *in vivo* studies would then be required. With the passage of the 1984 amend-

ment, the granting of deferrals ceased, as the amendment required a demonstration of bioequivalence for approval.

The biopharmaceutic regulations (17) specified that blood level and/or urinary excretion studies must be conducted when possible. When such studies were not considered to be feasible, alternative pharmacodynamic studies could be employed to demonstrate BA/BE. Should neither blood level/urinary excretion studies nor pharmacodynamic studies be feasible, full clinical studies were required. As pharmacodynamic measurements proved to be difficult to interpret, the only bioequivalence-based approvals using a pharmacodynamic approach employed the Stoughton–McKenzie test (for the topical glucocorticoids) (18–21). Attempts to use skin-stripping to develop a pharmacokinetic curve did not pass muster.

EVOLUTION OF THE BIOAVAILABILITY DECISION RULES

The early determination of bioequivalence employed the Canadian $\pm 20\%$ rule, i.e., the mean of AUC of the generic had to be within 20% of the mean AUC of the approved product. At first this was determined by using serum *versus* time plots on specially weighted paper, cutting the plot out and then weighing each separately.

However, following a National Academy of Science symposium in December 1971 in Washington DC (22), which addressed the subject of bioavailability, FDA began to employ the power approach. It routinely required AUC (determined by integration) and C_{max} measurements, approving products in which the means were $\pm 20\%$ of the innovator product within an 80% probability.

This worked well for drugs that largely remained in the central compartment. But Dr. Bernard Cabana, Director of the Division of Biopharmaceutics, observed that highly variable drug products, i.e., those with a coefficient of variation greater than 35%, failed this conventional bioequivalence test, even though the individual data were much the same. He and John Harter, MD, developed the 75/75 (sometimes called the 75/125) rule, under which bioequivalence would be met if:

- The relative bioavailability of the Test Product to the Reference Product exceeded 75% but was less than 125% in at least 75% of the subjects studied.
- There was no more than 20% difference in mean C_{max} and AUC.

This effectively obviated the negating effects of outliers.

But Haynes (23) demonstrated that the rule had undesirable performance characteristics and lacked statistical underpinning.

Following a meeting with Westlake, FDA Statistician, Don Schuirmann and the Division of Biopharmaceutics, we resolved the issue by withdrawing the 75/75 rule, on the basis that it lacked statistical underpinning. Eventually we implemented a procedure developed by Schuirmann, called the “Two One-Sided Test Procedure” (24,25). This 90% confidence interval approach recognizes that no two treatments will have exactly the same peak and area values and is based on the premise that the difference between the test and

reference products is less than 20%, inasmuch as industry, academia, and the regulatory agency agree that a difference of 20% is not clinically significant.

A more recent procedure, *Individual Bioequivalence* (26) based on a within-subject comparison of test and reference product ratios, had been considered, but not adopted by the Agency.

BATCH-TO-BATCH BIOEQUIVALENCE ASSURANCE

During the review of ANDA’s for generic drugs we observed that occasionally the generic formulation was considerably more bioavailable than the NDA product. By way of example, several generic companies submitted data showing their triple sulfa suspension to be about 40% more available than the innovator product. Both FDA and the innovator company conducted studies to establish the cause. Eventually it was determined that the etiology of this inequivalence was a prior reformulation of the sulfadiazine component of the pioneer formulation resulting in a decrease in bioavailability. This information along with the digoxin episode where the bioavailability of two different lots marketed by the same generic company differed by over 100% convinced me of the need for a lot-to-lot test that would provide assurance that there were no inter-lot bioavailability changes. A review of the Wagner and Levy data provided in John Wagner’s contract reports indicated that the dissolution test offered the best and most efficient method of accomplishing this.

Much of our subsequent work employed John Poole’s rotating paddle method (27), which used a three-neck resin flask and a rotating paddle at a speed of rotation of 50 rpm. This procedure generated essentially the same dissolution profile as the USP Basket dissolution method rotating at 100 rpm. Data generated by and submitted to the FDA established that this procedure was more reliable and exhibited less tablet-to-tablet variation than the USP rotating basket. This was also true of data submitted under various FDA (i.e., Division of Clinical Research) contracts as well as data submitted through the ANDA process.

With the bio-inequivalence, of digoxin established by two different researchers, The Center Director and I were able to convince the FDA General Consul to reclassify digoxin as a new drug (28–30). The Federal Register announcement of this proposal included not only *in vivo* bioequivalence testing but also a rigorous dissolution test patterned after the Poole method. However, Commissioner Schmidt (a cardiologist) “stayed” the enforcement of this regulation (31), because Burroughs Welcomes Lanoxin® did not exhibit any bioequivalence problem. The *staying of this regulation* has never been changed. The net result is that the attempt to reclassify digoxin and digitoxin as “New Drugs” resulted in the dissolution testing of 12 tablets as the only market entry requirement (32). The test specified in the Federal Register, which set forth the criteria for marketing these glycosides, was Poole’s paddle method run at 50 rpm. If the tablet dissolved more than 95% in 1 h or 90% in 15 min, a New Drug Application would have to be filed.

This regulatory action was opposed by the USP because they had just instituted a requirement employing the USP rotating basket method run at 120 rpm, with a minimum of 65% dissolved in 1 h (33). Data generated by FDA

Laboratories and FDA Extramural Contracts indicated that 120 rpm was too fast, obviating differences in generic product dissolution. Two years later, the OTA report noted that “the dissolution tests which had been specified in the compendia since 1970, are carried out in an apparatus that may introduce extraneous sources of variation in the dissolution process.” It also noted that the compendia acceptance criteria resulted in poor protection. They pointed out that “only when the percentage of defective units in a batch is 60% or greater, do these requirements offer high assurance of detecting defective batches.” The end result was a standoff. USP maintained their test and specification for monitoring products in the marketplace, while FDA maintained theirs.

The individual batch testing to assure uniform lot-to-lot BE in the case of digoxin generated an intense argument. One clinical academic consultant to FDA insisted on a requirement that each generic batch be clinically tested in a small number of human volunteers. Another highly talented kineticist feeling the clinical requirement was too onerous pushed for testing each generic batch in beagle dogs. On the basis of the data collected, I argued for dissolution, using the procedure published in the Federal Register. The employment of the dissolution test as a method of assuring batch-to-batch equivalence, once bioequivalence had been established, was agreed upon following a profound discussion between Associate Commissioner for Medicine, Mark Novitch, Clinical Pharmacologist, John Harter, Pharmacokineticist Bernard Cabana, and myself. This approach, by that time, had been tested on a number of other drugs, by obtaining batches of different generic drug products and testing them and the innovator’s product in FDA labs. These were sent to the USP for incorporation into the pharmacopoeia. Many were incorporated, but a number were not, or changed to the USP basket, rather than the paddle. Where the FDA would allow dissolution data alone to serve as a basis for product reformulation, the test employed had to be FDA’s paddle procedure; the standard for batch-to-batch testing was USP’s. The Division of Biopharmaceutics kept a “Blue Book” with the two sets of standards and chemists in the clinical divisions would refer to it in monitoring reformulation requests.

Part of the problem was that the rotating basket had not undergone the rigorous development that Poole’s rotating paddle had. Also, Poole’s procedure, instead of using a beaker like the basket method, employed a three-neck, round-bottom flask, which permitted easy sampling and temperature monitoring. It was, however, difficult to use. The basket on the other hand did not prevent the less cautious from placing the rod suspending the basket at a slight angle generating an artificially high dissolution response. Additionally, it was possible to generate widely varying results, even on a good product, because of the placement of the tablet in the bottom of the beaker. The flask method assured that the tablet would be at the center of the bottom, thereby generating a more uniform profile. To address the manipulation problem, I proposed that any *in vitro* data submitted in an NDA would have to be developed in concomitance with a demonstration of instrumental proficiency, using “test preparations” with known dissolution characteristics (33). This was eventually established as a standard requirement.

Additionally, FDA’s National Center for Drug Analysis undertook a thorough study of dissolution issues, finding that exposure of tablets to laboratory humidity, or vibration, could radically affect results (e.g., prednisone tablets). They also found that beakers had very uneven internal surfaces, which affected the process. Additionally, the official USP dissolution apparatus was a single unit. Since the specification required the dissolution of six dosage forms, slight differences in the speed of rotation were noted. NCDA built a gang of six dissolution devices which employed round-bottom beakers with machined internal surfaces. This chain-driven device also provided uniform rotation in each beaker. This is now a standard laboratory procedure.

PHARMACOKINETICS AND DRUG METABOLISM

In 1975, Dr. Cabana was appointed as the Director of the Division of Biopharmaceutics. This academically trained (Buffalo) and experienced (Bristol Meyers) pharmacokineticist established an outstanding research laboratory and began to tackle the many scientific problems facing the biopharmaceutic submissions in NDA’s. Key issues, e.g., drug metabolism, first pass effects, oxygenase effect on metabolism, and approval of controlled release drug products, were addressed. In the latter case, limits were set on the fluctuation between the peaks and valleys observed in the blood level *versus* time curves when comparing the controlled release product to repeated administration of the immediate release formulation. When large peak to trough fluctuations occurred in the blood level *versus* time curve, pharmacodynamic data were additionally required in lieu of clinical studies. Slowly the division succeeded in convincing FDA clinicians to employ pharmacokinetics in lieu of clinical studies when appropriate.

Because the Division of Biopharmaceutics was still subject to hiring and personnel freezes, it was significantly understaffed. Therefore, even though Dr. Cabana’s experience was in an antibiotic company, the pharmacokinetic and bioequivalence review of antibiotic formulations remained with the Division of Microbiology. There, bioequivalence was determined on the basis of a single blood level taken at a specified time point. Following the publication in JAMA of the bio-inequivalence of a newly approved generic tetracycline dosage form (34), the commissioner’s office transferred all pharmacokinetic review to the Division of Biopharmaceutics.

In spite of attempts to prepare guidelines for industry employment in biopharmaceutic studies, the official biopharmaceutic guideline for approval of controlled release products using pharmacokinetics in lieu of clinical data had a serious flaw. It failed to require a fed/fasting study. This became apparent when an application for 24-h theophylline was filed employing the new guidance. This was under FDA review at the time that the Center for Drug Research and Review (CDER) and the Center for Biologic Research and Review (CBER) were being merged following the retirement of CDER’s senior management team, i.e., Director and Deputy Director. The intent of the new management team was to dissolve the Division of Biopharmaceutics and the Biopharmaceutic Research Program as no longer serving a necessary function.

This also occurred at the time Cabana resigned his position and I became the new Director of the Division. With the change in authority, the Biopharmaceutics Review Branch recommended approval of this 24-h controlled release theophylline dosage form. My supervisory review reversed the recommended approval, because I detected dose dumping when the product was given with food, and referred it for definitive review by the Division's Pharmacokinetics Branch. The ANDA applicant, however, thinking the product approved, began to discuss the product in various forums. Unaware that the approval was inappropriate and had been reversed at a higher level, Drs. Weinberger and Hendeles tested the new product in an *in vivo* fed/fasting bioequivalence study (35). The dose dumping that occurred resulted in toxicity and at least one hospitalization.

With the reversal, the ANDA applicant complained to congress and a full congressional investigation was initiated by Congressman Dingle of Michigan. Simultaneously, Dr. Kelsey, now the Director of Scientific Investigations, determined that there had been several violations in the filing of the ANDA. While the Division's decision was scientifically correct, this rip roaring episode ended all discussion of dissolving the Division. Clearly, it was serving a needed purpose.

I convened a public workshop with the co-sponsorship of FDA, AAPS, DIA, and ASCPT (36) to address the issue of the BA and BE determination of controlled release products. At this point, Agency clinicians were pushing for full blown clinical studies. Professors John Wagner, Leslie Benet, and Gerhard Levy persuaded them that pharmacokinetics could be employed for these studies. This workshop was a tremendous success from the pharmacokinetic point of view, but failed to adequately address the issue of lot-to-lot monitoring using dissolution. It was followed by a second workshop (37). This batch–batch uniformity testing for assuring bioequivalence was also an issue for cream and ointment dosage forms. Workshops were held to address that issue (38) as well as percutaneous bioavailability and bioequivalence (39). Because of questions about the analytical methodology employed in conducting these studies, it too was explored in a separate workshop (40).

SCALE-UP AND POST APPROVAL CHANGES

Following the inspection experience with the cardiac glycosides, FDA established a rule requiring that batches produced for BE testing had to be manufactured in production size lots and on production equipment. Lacking the personnel to assure this, FDA accepted a statement to this effect in each ANDA. An FDA inspector dealing with another issue observed one company trying to scale-up a drug, on which they had received approval, from 100 to 1,000,000 tablets. The company, which developed several formulations of 100 tablets each and tested them in small groups of volunteers, found that one formulation met the BE requirement and submitted the data with the required statement.

In a meeting with generic manufacturers, FDA defined a production lot as 100,000 units or 10% of the production batch if it exceeded 1,000,000 units. Additionally it became clear that the modifications needed to be made to accommodate the larger batch size would violate the then existing

CMC data in the ANDA. Since FDA lacked the knowledge as to the type of changes that could be made and not affect the products absorption characteristics, a series of public workshops were held (41–43). An invaluable result of these workshops was the publication of batch size scale-up and allowable formulation and manufacturing changes as well as the testing requirements that could be used to justify them. The FDA tested these conditions at the University of Maryland, where Professors Shangraw and Augsberger demonstrated that the published conditions were conservative.

PUBLIC INTERACTION

Division of Biopharmaceutic personnel have routinely participated in scientific seminars and symposia sponsored by interested groups. The purpose was two-fold: to keep the public informed of anticipated government action and to get knowledgeable input on topics under consideration. The annual IIPAC at the University of Texas, Land-O-Lakes Conference at the University of Wisconsin, and the Management Conference at Purdue University were very helpful in the evolution of FDA's Biopharmaceutic Program and in keeping the pharmaceutical public aware of FDA developments. In addition, FDA's biopharmaceutists and pharmacokineticists have participated as committee members, speakers, and symposia chairs in various societies, e.g., AAPS, ACP, ASCP, DIA, *etc.* These conferences and societies were very helpful in developing constructive criticism and as an aid to problem solution, or at least a narrowing of the focus so that a problem could be more easily addressed.

PROFESSIONAL DEVELOPMENT

The decision to establish a Division of Biopharmaceutics was made with a commitment to hire trained staff. The freezes imposed by the President negated this approach. FDA management decided in lieu of hiring to develop staff. Given FDA's constant lack of resources problem, this has been a difficult path to follow. One reason for having a separate division rather than assigning the pharmacokineticists to the respective clinical divisions, as was the case with the pharmacologists, chemists, and consumer safety officers, was to facilitate this professional development. The splitting of the division did occur after my retirement in 1993, but not before we instituted a major effort to upgrade the training of the staff, thanks to Ralph Shangraw, Larry Augsberger, Gordon Amidon, and Thomas Ludden.

Eventually the division was split into several review divisions under the office of Clinical Pharmacology. It has been a difficult but fascinating journey. Where we are today is the result of the effort of the pioneering scientists and dedicated service of personnel in FDA, without whom the safety and reliability of our therapeutic arsenal would not be at the level we have come to expect.

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