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The Clay Feet of Bioequivalence Testing*

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Introduction

Much progress has been made since the concepts of bioavailability and bioequivalence were first defined. Advances in pharmacokinetics, biopharmaceutics, drug analysis including stereospecific assays, statistical methodology and regulatory policies have made their impact. The characteristics of the generic pharmaceutical industry have changed: manufacturers are larger due partly to consolidation and partly to the extension of a number of innovator companies into generic manufacturing, and the professional calibre and sophistication of the relevant scientific personnel as well as the quality of the manufacturing facilities are now generally comparable with those of the innovator companies. A small criminal element in the generic pharmaceutical industry has been brought to justice and their very few collaborators in the US Food and Drug Administration have been identified and removed. While these views come from a North American perspective, it is reasonable to assume that they and the comments that follow apply to most if not all developed countries. There are, however, some unresolved problems that require urgent attention if only to assure the credibility of the bioavailability and bioequivalence testing processes.

The Concept of Bioequivalence Applies Equally to Generic and Branded (Innovator) Products

The purpose of bioequivalence testing requirements is to assure the switchability of a medication. This has largely been viewed as a matter of assuring that switching a patient's medication from an innovator's brand to a generically equivalent product is not associated with any significant change in safety and efficacy of the drug. Similar considerations apply to switching from one manufacturer's generic product to that of another manufacturer, which is occurring with increasing frequency due to intense economic competition in the generic industry and the expanding presence of health maintenance organizations and clinics that purchase and often dispense prescription drugs. Not generally appreciated is the fact that bioequivalence as an issue applies equally to generic and branded (innovator) products. In many cases, pharmaceutical dosage forms used in clinical studies in support of a new drug application are reformulated before being marketed. The reformulation is done usually to facilitate large volume manufacturing, to enhance stability, and for economic reasons. Sometimes the formulation remains essentially intact but the manufacturing equipment and site are changed. In each case, there is a regulatory requirement for bioequivalence testing. Thus, the biopharmaceutical performance of most branded as well as generic products is based on bioequivalence tests!

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The Clay Feet of Bioequivalence Testing

On the face of it, bioequivalence testing at this time is quite rigorous. Most studies and much of the data analyses are performed under contract by clinical research organizations with substantial experience in this area. There are, however, some astounding weaknesses in the process. The sponsor selects the particular lot of reference and test product to be used for clinical testing. This permits prior testing for in-vitro dissolution characteristics and dosage form content of active drug to enhance the likelihood of a favourable outcome of the clinical study. With respect to active drug content, even a difference of a few percent in favour of the test article can be sufficient to make an otherwise unacceptable difference in area under the drug concentration–time curve (AUC) between two products acceptable for regulatory purposes. This type of non-random and biased testing is contrary to all precepts of quality assurance. It can be easily corrected by taking the selection of test product samples out of the hands of the manufacturer and making the sampling truly random.

The Bottomless Pit of Quality Control by Dissolution Testing

Once the bioavailability or bioequivalence of a drug product has been demonstrated to be within regulatory limits, the performance of subsequent production lots, the stability of the biopharmaceutical (release) characteristics of the product as a function of time during storage, and even the acceptability of apparently minor formulation or manufacturing changes without clinical testing are assessed by in-vitro dissolution or drug release rate tests. Such tests are typically calibrated against the in-vivo drug release or absorption data obtained in the clinical study but, since only one lot of the test product was used, the acceptable limits of the dissolution test cannot be objectively determined. At present, these limits are set essentially arbitrarily. The lower limit of most in-vitro dissolution tests represents a potentially bottomless pit, being conservative in some cases and possibly disastrous in others. A dissolution test cannot serve as a meaningful quality control measure unless the acceptable range of relevant dissolution rate parameters has been properly validated.

From Here to Eternity

Unless the formulation or manufacturing conditions are changed significantly, the bioavailability or bioequivalence

of a product has to be demonstrated only once, i.e. when regulatory approval is sought. Over the years, subtle changes in the physicochemical characteristics of the drug and excipient components as received from the respective suppliers and some drift in manufacturing conditions may alter the in-vivo release characteristics of the drug product and affect its clinical performance. These changes may not be reflected adequately by the in-vitro dissolution test used for quality control and stability testing.

Another possibility is that the biopharmaceutical characteristics of a drug product are adversely affected by "real world" storage conditions, i.e. the changes in humidity and temperature to which capsules and tablets are exposed when a patient opens the container repeatedly. Do epileptic patients on carbamazepine have to experience seizures before it is realized that the bioavailability characteristics of carbamazepine tablets are adversely affected by humidity and that the first used and last tablets in a bottle may not be bioequivalent?

It is inconceivable that important oral drug products are not subjected to a "second look", biopharmaceutically, some time after their entry into the market. It does not make sense that one bioavailability or bioequivalence study before marketing should be sufficient from here to eternity. Unlike the active ingredient as a molecular species, a pharmaceutical formulation as a drug delivery system is a complex, heterogeneous entity which can be subject to many hard-to-recognize physicochemical changes that can affect its clinical functionality. Such changes, be they a function of time, subtle differences in excipient characteristics, or apparently minor or unrecognized alterations in manufacturing conditions, have the potential to affect the rate and extent of absorption of the active ingredient.

I propose that some time after the marketing of a newly approved innovator or generic pharmaceutical product requiring demonstration of bioequivalence, the relevant regulatory agency will obtain adequate quantities of several production lots of the product on the open market (pharmacy or wholesaler). In the case of a generic product, adequate quantities of several production lots of the reference (innovator's) product will be similarly obtained. The different materials may be subjected to dissolution tests and the material to be used for bioavailability assessment may be selected on that basis (for example, the middle or lowest ranked production lot in the dissolution test may be selected) provided that the reference product is selected on the same basis. If the product to be tested is an innovator's product, then the reference should be the production lot originally tested and the outcome of the "second look" bioequivalence study should be assessed in conjunction with the historical bioavailability and dissolution rate data as well as the present dissolution rate data for the originally tested production lot. These materials should be submitted to a regulatory agency-approved commercial clinical test laboratory for bioavailability testing under the same protocol as the one for the earlier, manufacturer-sponsored bioavailability test. Depending on the outcome of the regulatory agency supervised bioavailability study, the test product can be continued to be marketed or (if bioavailability is seriously impaired) must be recalled, reformulated, and retested. If the bioavailability defect is not serious, the manufacturer should not have to recall the product pending prompt reformulation and bioavailability assessment of the new formulation. For products with critical therapeutic indications, where inadequate bioavailability could have serious adverse effects on health, the bioavailability test procedure should be repeated at least every five years. The cost of regulatory agency-supervised bioavailability testing should be borne by the manufacturer. That cost will be, in most cases, considerably less than 1% of the annual sales of the medication.

Alone Together: Individual vs Average Bioequivalence

The bioavailability of an orally administered pharmaceutical product is a function of the intrinsic properties of the drug, the physicochemical characteristics of its dosage form and the physiologic environment of the gastrointestinal tract. Physiologic individuality of the gastrointestinal tract is expressed, among others, in differences in motility, transit rate, pH, composition and flow rate of bile, and activity of drug-metabolizing enzyme systems in intestinal tissue. This can result in subject-by-product interactions such that the bioavailability of a test product relative to that of a reference product may be consistently different between individuals. That would be of particular concern if the subpopulation representing the patient population using a particular drug product differs significantly from normal subjects with respect to relevant physiologic variables. Concern for this problem has led to proposals for a new approach to bioequivalence testing with a change in focus from average bioequivalence to individual bioequivalence. This requires that each product be tested (at least) twice in each subject and that the subjects represent, as much as possible, the target population for the drug. The difficulties, both statistical and practical, of implementing and interpreting the results of such studies are formidable but their rationale is substantial. Some simple steps can be taken immediately to help address this problem. To enhance the likelihood of switchability, test products should not only be subject to clinical bioequivalence testing but also to comprehensive in-vitro dissolution (release rate) profiling. This would mean dissolution testing over a range of physiologic pH (including initial exposure to simulated gastric pH), stirring rates, interfacial tension, bile salt concentrations, pancreatin, and the mix of bile salts and lipids found to simulate the food effect on certain controlled release dosage forms. If the reference and test products perform similarly under these diverse conditions, then at least a degree of reassurance in the context of individual bioequivalence assessment is obtained. However, it is premature to make in-vitro dissolution profiling a regulatory requirement in view of the presently limited experience with this strategy. Moreover, this type of testing does not address all aspects of physiologic individuality, particularly presystemic biotransformation.

Serious consideration must be given to clinically testing at least those oral drug products used for critical indications (anticoagulants, antiepileptics, antidiabetics and anti-infectives, among others) in target populations. Such testing can be carried out in a realistic setting, i.e. during regular drug administration to patients under normal conditions

(i.e. without standardization of food intake and other such variables).

The patients would be at steady state as reflected by one or two time-defined plasma concentration determinations per day every one or more days (depending on the elimination half-life) for several measurements. The medication would then be switched from the reference to the test material with continued regular monitoring of plasma concentrations. Depending on the drug, the focus would be on C_{min} (to assure efficacy) only or C_{min} and C_{max} (if that metric is related to efficacy or safety). The methodology would be based on quality control procedures generally used in manufacturing industries. Acceptable concentration boundaries would be set and the time course of either C_{min} or C_{min} and C_{max} would be followed by trend analysis.† If the test product escapes the boundary and this is determined to be a statistically significant trend, use of the test product is discontinued and the patient is switched back to the reference medication. There is no need to determine how inequivalent the test material is (i.e. it does not have to be administered until a new steady state is reached); it is sufficient to establish that the test product is not bioequivalent. If the drug concentrations stay within the designated boundaries, the necessary duration of test product administration is a function mainly of its elimination half-life, the relative magnitude of the acceptable plasma concentration boundaries, and the intra-individual variability of absorption and elimination kinetics. Thus, the duration of test product administration to assure bioequivalence will not be the same for every drug. As an option to account for possible temporal changes in a patient's physiologic status, some days of monitoring plasma concentrations after reinstitution of reference drug therapy can be added to the protocol.

Why Bother?

Not surprisingly, there is a reluctance by many in the pharmaceutical industry to consider revisions in regulatory requirements, particularly if such requirements are perceived, rightly or wrongly, to be more costly and time-consuming. Large bureaucracies, such as regulatory agencies, have their own inherent inertias. As one regulatory official (who favours change) recently put it to me: "People ask 'Where are the Bodies Lying in the Streets?' and when none can be pointed to they conclude that there is no problem." Well, there is a problem. It is one of bad science as it pertains to proper product sampling and other aspects of quality control in particular. Experience in clinical pharmacology has shown that the "bodies lying in the streets" can only be recognized by controlled, prospective studies except for some extreme cases. Moreover, there is an inherent bias against the discovery of bioavailability problems in particular lots of a branded product. To most physicians and consumers, the patient is taking the same medication irrespective of receiving different production lots of the product when a prescription is refilled. Inadequate therapeutic response or adverse effects occurring after prolonged use of a branded product tend to be attributed to a change in the patient rather than a change in the quality of the medication. The index of suspicion is much higher when the patient is switched to a nominally generic equivalent with a different physical appearance, and many such observations result in case reports in the literature.

The Challenge

The challenge facing us as pharmaceutical scientists is to recognize the current shortcomings of bioavailability and bioequivalence testing and to initiate the necessary changes. All of us recognize that there is a delicate balance between cost and benefit. Society cannot afford the measures required to achieve absolute assurance of bioavailability and bioequivalence nor is such objective attainable — scientists appreciate and accept the principle of residual uncertainty. The proposals outlined here are attainable and the costs would not be prohibitive. Will the pharmaceutical industry initiate the necessary changes in bioequivalence assessment because they are right and needed, or will the industry respond only to regulatory fiat? Most pharmaceutical industry executives object to what they believe to be excessive regulatory requirements—their best argument against such requirements is to show that they will make necessary changes in areas such as bioequivalence testing on their own initiative, without being strong-armed by government.

Conflict of Interest Statement

Professor Levy is a consultant for and owns stock in several pharmaceutical companies. On the other hand, he and his family use prescription drugs, both branded and generic, and pay for them. Also (conflict of interest matters are sufficiently complex to require more than two hands), he is a tax payer and realizes that his taxes pay in part for public health care services, including medications.

†There has been considerable discussion concerning the most suitable metrics for bioequivalence testing, almost exclusively in connection with single-dose testing. A corresponding assessment for steady state (multiple dose) testing is indicated.