

28 December, 2006

Division of Dockets Management,
Food and Drug Administration,
Department of Health and Human Services,
5630 Fishers Lane, Room. 1061,
Rockville, MD 20852.

2007-0003

Citizen Petition

The undersigned submits this petition under 21 CFR 320.1-320.6 of the Federal Food, Drug, and Cosmetic to request the Commissioner of Food and Drugs to issue guidelines on **Risk-Based Bioequivalence Testing**.

A. Action requested

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process.² The showing that must be made for an ANDA to be approved is quite different from what is required in a new drug application (NDA). An NDA applicant must prove that the drug product is safe and effective. An ANDA does not have to prove the safety and effectiveness of the drug product because an ANDA relies on the finding FDA has made that the reference listed drug is safe and effective. Instead, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the reference listed drug (21 U. S.C. 355(j)(2)(A)(iv)). The scientific premise underlying the Hatch-Waxman Amendments is that in most circumstances bioequivalent drug products may be substituted for each other.

A generic drug is bioequivalent to the listed drug if "the rate and extent of the absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses" (21 U.S.C. 355(j)(8)(B)(i)).

The 21st Century Initiative by the US FDA has resulted in several major changes in how the US FDA would conduct its business in the future. This includes the ONDC's Risk-Based Quality Systems and the Risk-Based GMP Initiative. Bioequivalence testing of multisource drug products occupies a significant portion of ANDAs filings and the US FDA has recently initiated several actions to streamline the bioequivalence trials; these initiatives include "Waivers of *In Vivo* Demonstration of Bioequivalence, the "Biopharmaceutics Classification System." However, there remains a need to open the entire issue of bioequivalence testing in light of formal risk-based testing requirements.

Over the past quarter of a century, the protocols used for the testing of bioequivalence have been based on assumptions that are no longer considered valid scientifically; the primary argument adduced here is that the responsibility of the multisource drug manufacturer ends if the product is equivalent to the innovator's product in its ability to deliver the active drug to the body. The thermodynamic activity of the active drug at the intended site of absorption is the only critical parameter that should be sufficient to

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establish bioequivalence. The universal use of blood level studies to demonstrate bioequivalence is flawed on many counts. It serves as a surrogate for the concentration of drug at the site of action, which in itself is a hypothetical surrogate for the pharmacological response, which in turn is another hypothetical surrogate for the clinical response—the end point of equivalence demonstration. The inherent variability in the relationship between the pharmacological response and the clinical response is large and often not well understood; the inherent variability in eliciting a pharmacological response and the concentration of drug at hypothetical site of action is highly variable and not well understood; the inherent variability in the concentration of active drug at the hypothetical site of action and blood or plasma levels is in most cases conjectural and highly variable when it does count. This statement is not to be construed as questioning the dose-response relationship, instead it questions the use of blood levels in establishing equivalence in the “rate and extent of drug absorption” and to correlate this with the ultimate goal of establishing therapeutic equivalence. In reality, the least variable relationship exists between the thermodynamic activity of the active drug at the site of administration and its blood levels. The question arises whether it necessary at all to make the blood levels as a surrogate for the efficiency of the drug delivery systems?

The current requirements of bioequivalence testing further jeopardize the quality assessment of multisource drugs since the testing to establish equivalence is only required at the time of ANDA filing and when there are substantial changes made to the process of manufacture.

There is therefore a need to establish new rules for risk-based bioequivalence testing, the subject of this petition to allow faster approval of multisource products, better control on the quality of these products and above all a substantially reduced cost to consumers.

B. Statement of grounds

The true spirit of the law that established multisource products is to assure that the differences in the drug delivery systems are not significant enough to produce a different therapeutic response. The multisource products first establish chemical equivalence and where a pharmaceutical equivalence is also established, the remaining variability is inherent to both the innovator and multisource drug product. A risk-based bioequivalence testing requirement would determine if methods exist to prove that the thermodynamic activity of the active drug is equivalent at the site of administration. Tests to study this are cheaper to conduct and their continued use in the batch releases further assures consistent quality. The most widely used test of dissolution has served the purpose well for decades. The USP currently requires dissolution tests as measures of in process quality control for many drugs. Unfortunately, the science of dissolution testing has not progressed to where it could be more predictive of the thermodynamic activity of drugs that will directly correlated with absorption pressure.

This petition request the US FDA to take a bold initiative in requesting comments on how modifications to dissolution testing can be used to substitute bioequivalence submissions and then require that these tests be conducted for the purpose of batch releases to assure ongoing assurance to drug delivery to the body.

Whereas a large number of modifications to dissolution methodologies, the dissolution media and methods of testing have been reported in the literature, use of multiphasic

dissolution systems that will characterize the thermodynamic activity of drug at the site of absorption have not been fully developed. These simple systems are likely to simulate the absorption surface better than the use of more elaborate models, ranging from PAMPA to Caco-2 systems. Once the dissolution medium is capable of picking up the difference in the transport of free drug molecules across a lipophilic barrier, the thermodynamic activity is established and when compared to the innovator's product, the responsibility of demonstrating equivalence by the multisource product manufacturer ends since from this point forward, all factors will apply equally to both products.

Instant Release Dosage Forms:

The US FDA allows waiver of bioequivalence for several drugs; this should continue and the list expanded to include those where there is a sufficient merit in the actual use of the product over period of time. For all other products where the US FDA currently requires demonstration of bioequivalence, the multisource product manufacturer will be allowed to present dissolution data in a multiphasic model as described above to show that indeed the thermodynamic potential achieved from the generic dosage form is identical to that observed for the innovator product. It is likely that for most of the products for which demonstration of bioequivalence is required will no longer need it. In those instances where the drug delivery system is substantially different from the system used by the innovator, full bioequivalence testing will be required.

Modified Release Dosage Forms:

The concept of demonstrating equivalence of thermodynamic potential applies identically to these dosage forms as well, except there the multisource drug product manufacturer would need to show a time-function analysis as well and compare it with the innovator product. In those instances where the generic product has a different mode of drug delivery, full bioequivalence testing will be required.

Effect of Food

Special studies are required to study the effect of food on drug absorption, adding substantial cost to the submission of ANDAs. Such studies can be rendered obsolete when the innovator product is compared to the generic product unless in those situations where the drug delivery systems is substantially different from that of the innovator. The argument presented here is universal to the petition that all those factors which are common to the two dosage forms need not be tested.

Topical Drugs

A lot of current controversy on the design of bioequivalence testing protocols can be obviated through development of release models across the base of dosage form; any variations due to penetration across skin should not be part of the evaluation. Standard dissolution models do not work well for this simulation and much work would be needed to establish an acceptable model.

Inhalation Drugs

Obviously, there will be many situations where it will not be possible to demonstrate such equivalence of thermodynamic activity; for example, in the case of inhalation

products where the size of impacted particle is highly variable and dependent on the dosage form design; here the testing of blood levels will be inevitable.

Biological Drugs:

The use of thermodynamic activity as a measure of equivalence provides another remarkable opportunity to solve the current dilemma of establishing equivalence of biological products. The US FDA is developing guidelines for "biosimilar" or "follow-on" biological products and has not been able to conclude what tests would constitute demonstration of bioequivalence. Whereas these products are administered through routes that provide lesser barriers in the entry of drug to the body, the differences are related to antigenicity potential which needs a clinical evaluation; however, studies have demonstrated that minute differences in the structure of protein drugs including dimerization, 3 and 4th degree structures and easily picked up in partitioning studies since these studies truly represent the thermodynamic potential which is readily changed even where minor differences in the structures, often too small to be detected by even the most sophisticated instruments; in most instances, the use of instrumentation itself disturbs the structure enough to make the studies meaningless. This almost borders on the Heisenberg's principle of uncertainty.

Botanical Drugs

Whereas the US FDA has not yet approved product under this category, this will happen soon and then the question will arise how to evaluate their equivalence; since surrogate markers are used in lieu of active moieties, which are not generally well-established, it will be difficult to develop any model including the bioequivalence model to prove equivalence of these products. This is one category where some clinical testing would be inevitable.

This petition requests the US FDA to open a larger discussion and invite comments in the creation of novel dissolution systems that can be used to establish bioequivalence for all products where demonstration of thermodynamic activity is feasible. This is not an attempt to extend the IVIVC concept since the basis presented here is to move away from in vivo measurements.

C. Environmental impact

There is no environmental impact issue involved in this petition.

D. Economic impact

The economic impact of this petition is very large; currently, the largest cost involved in the regulatory filing for the multisource drug product manufacturers is the conduct of bioequivalence testing. Even when these filings include the bioequivalence testing, the ongoing demonstration of bioequivalence is not possible and that might adversely impact on the cost-effectiveness of generic drug products. By adopting the risk-based bioequivalence testing and allowing the multisource drug product manufacturers to devise tests that can be submitted in lieu of bioequivalence testing, the cost of generic drugs will reduce substantially and an ongoing assurance of therapeutic equivalence made available through use of these newly developed tools in the in-process control of drug manufacturing. A large number of foreign manufacturers will then be able to participate in qualifying for manufacturing in accordance to the US FDA cGMP

standards and the competition in pricing will bring down the cost of drugs to the US consumers, who are currently paying the highest cost of drug treatment in the world.

The suggestions made in this petition has strong scientific basis and the petitioner has decades of experience in designing these tools as suggested and would be pleased to participate in this initiative of the US FDA. [A list of relevant books authored by the petitioner is appended here].

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.



Sarfaraz K. Niazi, Ph.D.
Foreign Professor, HEJ Research Institute
Head, Center for Bioequivalence Testing,
International Center for Chemical and Biological Sciences
Karachi University, Pakistan

And

CEO, Pharmaceutical Scientist Inc
20 Riverside Drive
Deerfield, Illinois 60015

Relevant books authored by the petitioner

1. Textbook of Biopharmaceutics and Clinical Pharmacokinetics. J Wiley & Sons, New York, NY 1979
2. Handbook of Pharmaceutical Manufacturing Formulations, Six Volumes, CRC Press. 2004, Boca Raton, FL
3. Handbook of Biogeneric Therapeutic Proteins: Manufacturing, Regulatory, Patent and Testing. CRC Press 2004, Boca Raton, FL
4. Handbook of Preformulation. InForma 2006, New York, NY
5. Handbook of Bioequivalence Testing., InForma 2007, New York, NY