

FDA Bioequivalence Standards for NTI Drugs
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The FDA's policy on bioequivalence is currently under scrutiny by its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. The Advisory Committee has proposed tightening the FDA's bioequivalence standards which would change the way generic medications with a narrow therapeutic index (NTI) are approved.¹ Narrow therapeutic index drugs are defined as "drug products containing certain drug substances subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation."² Such medications include, but are not limited to, warfarin, digoxin, lithium, phenytoin, and theophylline. Presently, NTI drugs are approved in the same manner as all generic medications. The debate focuses around the fact that NTI drugs can potentially cause more severe consequences, specifically when different brands are interchanged, thus suggesting stricter approval criteria.

According to the FDA's Guidance for Industry, its current process for determining bioequivalence (BE) for NTI drugs, as well as all other medications, is the same unless otherwise stated in a specific guideline.² To establish BE, the manufacturer of the generic drug must demonstrate the drug is bioequivalent to the innovator drug.³ The FDA requires that the average peak plasma, serum, or blood concentration and the average area under the concentration-versus-time curve of a generic drug product have a BE range between 80-125 percent of the C_{max} and AUC values of the brand name product.¹ Bioequivalent drugs normally confer an AB rating. This rating indicates that actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence.⁴

All but one adviser agreed that the FDA should produce a list of NTI drugs and consider them as an independent class of medications. They also acknowledged the fact that if such restrictions were to be placed on this group of medications, manufacturer's cost of production of generic medications would ultimately increase due to the need of a larger study population to satisfy more stringent requirements.¹ The FDA has discussed this issue several times in the past. In 1997, the National Association of Boards of Pharmacy contacted the FDA in regards to their position on generic drugs and their substitutability. Roger L. William, Deputy Center Director for Pharmaceutical Science at the Center for Drug Evaluation and Research, responded that, "because of FDA's strict bioequivalence criteria, we believe that drugs do not fall into discrete groups that would allow one to consider NTI drugs as being clearly different from other drugs for purposes of therapeutic substitution. No data has been submitted to FDA to cause any revision in the bioequivalence criteria for these products. Therefore, there has been no scientific or regulatory purpose at this time for the agency to create and implement a mechanism to designate some products as being narrow therapeutic index products, or to define any other specific group of products."⁵

The FDA has analyzed many studies to prove that their current criterion is sufficient in determining bioequivalence, citing a disconnection between the FDA and some in the medical community. The FDA has reported that after reviewing more than 2000 bioequivalence studies, the average variation in AUC and C_{max} from the innovator drug product is a mere 5% differential. The FDA also has also analyzed studies that highlighted physicians and patients beliefs that generic products are not always equivalent to innovator drug products. The FDA noted that many physicians are unaware of the FDA's approval process for generic medications as indicated by a study that revealed less than 1 in 5 physicians could recall the FDA's

bioequivalence standards. The FDA hopes to move slowly in its decision making process and has made no agreement in regards to new standards for NTI drugs.¹

References

1. Traynor K. FDA mulls changes to bioequivalence standards. *Am J Health-Syst Pharm.* 2010; 67:864
2. FDA Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>. March 2003 (Accessed 22nd June 2010).
3. FDA Ensures Equivalence of Generic Drugs. US Food and Drug Administration. <http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismAndDrugPreparedness/ucm134444.htm>. Accessed June 22, 2010.
4. APPROVED DRUG PRODUCTS with Therapeutic Equivalence Evaluations. US Food and Drug Administration. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf> approved drug products with therapeutic equivalence. Accessed June 22, 2010.
5. Therapeutic Equivalence of Generic Drugs - Response to National Association of Boards of Pharmacy. US Food and Drug Administration. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073224.htm>. Accessed June 22, 2010.