



U.S. Food and Drug Administration  
Center for Drug Evaluation and Research

## Therapeutic Equivalence of Generic Drugs Response to National Association of Boards of Pharmacy

April 16, 1997

National Association of Boards of Pharmacy  
Attention: Mr. Carmen A. Catizone  
Executive Director/Secretary  
700 Busse Highway  
Park Ridge, IL 60068

Dear Mr. Catizone:

I am responding to your letter of March 18, 1997, to Mr. Douglas Sporn, Director, Office of Generic Drugs (OGD), that inquires about the position of the Food and Drug Administration (FDA) on narrow therapeutic index (NTI) drugs, and their substitutability. As you are aware, in the process of evaluating applications for generic drugs, the FDA makes recommendations via a document entitled *Approved Drug Products with Therapeutic Equivalence Ratings* (the *Orange Book*) that approved multiple source drug products, including NTI drugs, are therapeutically equivalent. This term indicates that they can be substituted with the full expectation by the patient and physician that they will have the same clinical effect and safety profile as the innovator drug.

Before I respond to your four specific questions, I would like to briefly describe some important historical events and decisions that pertain to these questions and the FDA's current position. In a 1979 Federal Register notice, the Agency proposed the development of the *Orange Book* and definition of the criteria to be used by FDA in evaluating therapeutic equivalence. The *Orange Book* and the therapeutic equivalence criteria were finalized in 1980. Since then this publication has proven to be a constructive and important resource for all parties involved in the health-care delivery system, including, for example, manufacturers, physicians, pharmacists, hospitals, and federal and state agencies.

In 1986, FDA conducted a three-day public hearing to provide a forum to discuss the Agency's method of determining bioequivalence of generic drugs for immediate release, solid oral dosage forms. In addition to its use for generic products, the FDA method of determining bioequivalence is also used by innovator firms when their drug products are reformulated or certain other manufacturing changes are made. The goal of the workshop was to elicit data on claimed problems with the method of determination of bioequivalence. There were fifty speakers and over 800 participants. The meeting was chaired by former Commissioner Frank Young, M.D. In addition, three outside eminent scientists participated as expert consultants. The agenda of the hearing consisted of five topics that were broken down into sub-topics. One of the topics, the "Design of Bioequivalence Studies" included a sub-topic relevant to the issues you have raised: "Should FDA Develop Individual Criteria for Each Drug or Class of Drugs?"

Commissioner Young, subsequently, appointed a Task Force to analyze the issues raised at the hearing and make recommendations for actions the Agency should take concerning its bioequivalence program. Among the task force conclusions was: "FDA is prepared to use a more stringent criterion if differences of this size [e.g., the 90% confidence interval for the ratio of the

test product mean AUC to that of the innovator must lie entirely within the interval (0.80-1.20) (now 0.80 to 1.25 on log transformed data)] are shown to be clinically significant." No clinical data has been submitted to the Agency in the ten plus years since the hearing that would warrant the Agency narrowing the present confidence interval of 0.80 to 1.25 on any drug or class of drugs. If a tighter statistical interval was used for NTI drugs, it is even possible that if an innovator firm reformulated its product, the product might not be bioequivalent to itself.

Subsequent to the hearing, two relevant studies were conducted on a drug thought to have a narrow therapeutic index, carbamazepine. These were done at the University of Tennessee and at Wake Forest University. Neither study could demonstrate problems with bioequivalence between innovator and generic products nor a difference in the efficacy or safety profiles.

Using the FDA bioequivalence criteria, the first 224 post-1962 drugs approved over the two year period after the Waxman Hatch amendments were passed, including some NTI drugs, had an observed mean bioavailability difference between the generic and innovator products of only 3.5%.

The above background is necessary to fully understand my responses to your four questions as follows:

**1. Is there an official FDA or government agency category of narrow therapeutic index drugs?**

Currently, the NTI designation is not a formal designation by the FDA. A list of so called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research in order to assist the FDA District Offices in their testing program that came about because of problems with the generic industry in the late 1980's. This working list of drugs is also currently being used as one of the factors to determine if an *in vivo* study or other data are needed to determine the impact of **post-approval** changes in the manufacture of a drug product. The list is in the "Scale-Up and Post-Approval Changes for Intermediate Release Products" (SUPAC-IR) guidance document and is used in conjunction with other factors such as drug permeability and solubility to assess the impact of changes made after approval.

In 1990, the Acting Commissioner of the Food and Drug Administration, in a letter to the Pennsylvania Department of Health said that the FDA does not formally designate narrow therapeutic index drugs either in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" or elsewhere.

**2. Do you plan to develop a formal list of "NTI" drugs?**

Narrow therapeutic **INDEX** is a term of art which has come into current use, including use by the agency. The term, more correctly, is narrow therapeutic ratio. Narrow therapeutic ratio is defined in the regulations at 21 CFR 320.33(c). This subsection deals with criteria and evidence to assess actual or potential bioequivalence problems. This ratio, as defined in the regulation, is one of a number of factors to be considered is

assessing these actual or potential problems. No listing of drugs is included in this regulation. At some point in the future, appropriate guidance could be developed based on this criterion to provide guidance to assess bioequivalence, potentially including a listing of drug products.

According to 21 CFR 320.33(c), narrow therapeutic ratio is defined as follows:

- a. There is less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or
- b. There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
- c. Safe and effective use of the drug products require careful titration and patient monitoring.

### **3. Is there a direct relationship between narrow therapeutic index and substitutability?**

FDA recognizes the scientific concept that drugs differ in their therapeutic range. However, 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. The FDA is now considering a different approach to documenting bioequivalence. This approach is termed 'individual bioequivalence.'

This approach allows the possibility of scaling the bioequivalence 'goalposts' (e.g., the boundary of 80 - 125%) based on variability of the reference listed (innovator) drug. One possible aspect of the approach may be that for certain drug products, which might be termed narrow therapeutic index or ratio drugs, the goalposts would always be scaled to the variability of the reference listed drug. This might have the effect of widening or narrowing the goalposts, depending on the performance of the reference listed drug. Examination of the new approach is based on improvements in our scientific understanding of how to document bioequivalence. It is not based on any information to suggest that any drugs in the marketplace, either innovator or generic, narrow therapeutic

range or not, are not performing as they should and as designated in the *Orange Book*.

**4. Are there any "A" rated drugs in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" that have a narrow therapeutic index?**

Yes, there are a number of "A" rated drugs products in the Orange Book that could be considered "NTI" drugs, e.g., carbamazepine and theophylline.

FDA is aware of the NTI initiatives that are occurring at the state level. These include, but are not limited to, the proposed legislation you mentioned, the lobbying of state Boards of Pharmacy, the establishment of an organization to oppose NTI substitution, and the proposals by the state Drug Utilization Review Committee(s) to require tighter confidence intervals than the present 80 - 125 and different study designs. To date, we have not seen data to support such proposed changes. FDA is also aware that the practice of pharmacy and medicine is regulated at the state level and not by the Federal Government. However, we feel that any change or desire to change FDA's bioequivalence standards should be based upon appropriate data.

Finally, FDA's position on drug substitution is summarized in the preface and introduction to the Orange Book. The evaluations on therapeutic equivalence are "prepared to serve as public information and advice to state health agencies, prescribers and pharmacists to promote public education in the areas of drug product selection and to foster containment of health costs." Also, "it does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another nor, does it conversely, mandate the products that should be avoided." If one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have FDA's assurance that the physician should see the same clinical results and safety profile. Any differences that could exist should be no greater than one would expect if one lot of the innovator's product was substituted for another.

We suggest that you consider providing this information to the members of your association.

Thank you for requesting the FDA position on this very important topic.

Sincerely yours

/s "RLW"/

Roger L. Williams, M.D.  
Deputy Center Director for  
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