CAVEATS

The NTI Debate

For more than a year there has been a significant effort underway to improve patient access to affordable drug therapy. This effort is directed at a small group of drugs considered to have a narrow therapeutic index (NTI). This national effort began as questions were raised about the methods used by the Federal Food and Drug Administration (FDA) to approve generically equivalent NTI drug products. It has since branched off into a state-by-state campaign to limit or prevent NTI drug substitution. This is a significant issue and one that may result in restrictions on the drug products available to patients.

The FDA's position on the approval of generic NTI drug products is clear and consistent. In October 1990, Acting Commissioner James S. Benson wrote a letter to the Pennsylvania Department of Health in response to a question regarding the approval of NTI drug products. He stated, "We recognize the scientific concept that drugs differ quite markedly in their therapeutic range. However, because of the FDA's strict bioequivalency standards, we believe that drugs do not fall into discreet groups that would allow one to consider 'narrow range drugs' as being clearly different from other drugs, from a substitution point of view. Therefore, there has been no regulatory purpose for the agency to create and implement a mechanism to designate some products as being of narrow therapeutic range."

To further clarify the FDA's position on the approval of NTI drugs, Roger L. Williams, M.D., deputy center director for pharmaceutical science at the Center for Drug Evaluation and Research, wrote a letter to the National Association of Boards of Pharmacy. In this April 1997 letter, Dr. Williams described some of the historical events surrounding the approval of generically equivalent NTI drugs and briefly discussed the FDA's current policy of generic drug approval. At the end of the letter, Dr. Williams

stated the FDA's position in unequivocal terms: "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 would be no greater than one would expect if one lot of the innovator's product was substituted for another."

In January 1998, Stuart L. Nightingale, M.D., associate commissioner for health affairs, wrote a detailed letter to address the state-by-state lobbying efforts that question the interchangeability of NTI drugs. In his letter, Dr. Nightingale discussed several important points emphasizing the FDA's methods to assure the quality of generically equivalent drug products. He stated, "Because patients may pay closer attention to their symptoms when a substitution of one drug product for another occurs, an increase in symptoms may be reported at that time, and anecdotal reports of decreased efficacy or increased toxicity may result. Upon investigation by FDA, no problems attributed to substitution of one approved drug product for another has occurred." Thus, we need to better educate our patients so that they understand that the substitution of generically equivalent drug products will not cause harm or change the efficacy of their drug therapy. Dr. Nightingale further stated, "It is not necessary for the health care provider to approach any one therapeutic class of drug product differently from any other class; when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration."

Despite FDA's position on the approval of generically equivalent NTI drugs, the issue was introduced to lawmakers in many states under many different masks. The underlying intent was the same: to limit or prevent the substitutability of FDA-approved, generically equivalent drug products that are con-

sidered to have a narrow therapeutic index. Most states have defeated such efforts, but Texas, Virginia, and North Carolina have implemented legislation that restricts the use of generic NTI drug products.

In Texas, legislation passed requiring that a prescription for an NTI drug may be refilled only with the same drug product by the same manufacturer that the pharmacist used when the prescription was last dispensed. If a pharmacist is out of stock of the drug product, he or she may refill the prescription using a generically equivalent drug product, provided the patient is notified at that time and the prescriber is notified within 72 hours. While the legislation does not directly prevent generic substitution, it does question the switchability of FDA-approved generically equivalent drugs. Currently, the Board of Pharmacy is charged with promulgating a list of NTI drugs that are subject to the new legislation. The list currently contains nine drugs: carbamazepine, digoxin, divalproex, sodium, levothyroxine, lithium, phenytoin, theophylline, valproic acid, and warfarin sodium. Interestingly, Texas pharmacists are not allowed to substitute products which are not determined to be generically equivalent (according to the *Orange Book*); thus, since some of the drugs on the list do not have generic equivalents, the new legislation will not effect their therapeutic use. It is unclear why such drugs were included on the list. However, their inclusion likely will cause confusion for pharmacists and physicians.

In Virginia, legislation passed that states a pharmacist may not substitute or interchange an NTI drug without the documented consent of the prescriber to the substitution or interchange. The Board of Pharmacy is to create a list of NTI drugs that would be governed by the law. To date, no list has been created and the debate continues about which drugs should be included on the list.

The legislation in North Carolina is more exacting. The law states that a prescription for an NTI drug shall be refilled using the same drug product from the same manufacturer that the pharmacist last dispensed under the prescription. However, a pharmacist may substitute a generically equivalent product provided that the patient and prescriber provide written consent. One interesting twist to the legislation is that a *refill* prescription includes a new prescription written at the expiration of a prescription, which continues the patient's therapy with an NTI drug. This means that once a patient begins with an NTI drug, unless both patient and prescriber give written consent, the therapy must continue with the same drug product from the same manufacturer for the duration of the treatment. This continuation will hold true even if the treatment will last for many years.

Legislative measures passed in the above states question the ability of the pharmacist and physician to treat patients adequately using current practice methods. In addition, these measures also call into question the approval processes used by the FDA. Pharmacists need to be aware that similar legislation has been considered in other states, but has been overwhelmingly defeated. Most legislative bodies agree with and support the FDA's position on the approval of generic NTI drug products.

The FDA has established stringent guidelines for the approval of both branded and generic products, which govern both *in vitro* and *in vivo* testing. One key issue concerns possible flaws in the methods used by the FDA to determine bioequivalence—the comparison of the bioavailability of one drug product to another drug product (i.e., generic as compared with brand-name drug products). The FDA currently uses “average bioequivalence,” which assesses the rate and extent of absorption of one drug product in a group of subjects and another drug product in the same group of subjects. The study design is a single, two-way crossover, usually done in healthy male volunteers. The data from

each drug product is analyzed and then compared with a standard range of acceptable values. For many drugs, the FDA determines that two drug products are bioequivalent if the ratio of their rate and extent of absorption (plus their 90% confidence interval) fall between 0.8–1.25, using log-transformed data. In practical terms, this means that drug products that differ in their rate and extent of absorption by greater than approximately 10% will not be approved as generic equivalents. It is important to understand that the range of 0.8–1.25 includes the mean of the data and the 90% confidence interval. Thus, it is not possible for a drug with a mean ratio of 0.8 or 1.25 (i.e. 80% or 125% bioavailable) to be considered generically equivalent to the brand product using these criteria. According to the FDA, a study was conducted examining the bioequivalence of over 220 drugs (including some NTI drugs). The study concluded that the mean difference in bioavailability between generic and brand drug products was only 3.5%.

The list of NTI drugs was originally developed by the FDA as an informal list to aid FDA district officers in their testing program. This list contains 24 drugs, 17 of which have FDA-approved generically equivalent drug products currently available. The FDA has stated clearly on many occasions that this list was not intended to question the substitutability of generically equivalent NTI drug products. The FDA has stated further that it does not believe, from a substitution point of view, that drugs fall into discreet groups that would require one to consider NTI drugs different from other drugs.

There has been much discussion regarding which drugs should be considered to have a narrow therapeutic index. While most clinicians will agree that many drugs used for acute and chronic care require careful monitoring by physicians and pharmacists, there is no universal algorithm that dictates care. Interestingly, a federal regulation (21 CFR 320.33(c)) states that an NTI drug is one that requires careful titration

with patient monitoring. In addition, there is less than a two-fold difference in the minimum acceptable toxic concentration and the minimum acceptable effective concentration for the drug. This two-fold range prompts an interesting discussion among some clinicians regarding the inclusion or exclusion of the NTI designation of a drug.

The topic of NTI drug substitution currently is being discussed by state lawmakers across the country. It is imperative that you let the legislative bodies in your state know what you think about the issue. Also, it is important to contact your state pharmacy board so you can learn of current or pending legislation in your state. This is not an innocuous topic, but one that will have widespread implications for the care of your patients and the cost of health care nationwide.

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