Substitution of Critical Dose Drugs: Issues, Analysis, and Decision Making

Critical Use

Critical Dose

Critical Bioavailability

American Pharmaceutical Association
The National Professional Society of Pharmacists
Introduction

Over the past few years, there has been controversy concerning the substitution of generic equivalents of certain brand name drugs and the Food and Drug Administration’s (FDA’s) standards for evaluating the bioequivalence of the generic forms of these critical dose drugs. To help clarify the complex issues surrounding the use and substitution of critical dose drugs, APhA assembled a multidisciplinary panel of experts and held a roundtable discussion on the issue. The results of that discussion and its analysis constitute this publication. This publication is intended to help health care professionals and organizations understand the important issues involved in the use and substitution of critical dose drugs and to enable them to make informed decisions regarding the use and substitution of these drugs in specific patients or patient populations.

The essence of the controversy involving critical dose drugs is whether the FDA’s standards regulating bioequivalence are strict enough to ensure that generic formulations of these drugs are clinically equivalent to their brand name competitors in terms of therapeutic outcomes. The brand name manufacturers of these drugs sometimes suggest that the current FDA standards are inadequate for critical dose drugs, whereas the FDA has vigorously defended those standards as being more than adequate. In addition, perhaps because they are so complex, these bioequivalence standards have been widely misinterpreted and misunderstood.

A host of issues surround this bioequivalence controversy. The whole concept that there is a special class of drugs deemed critical dose or narrow therapeutic index is new. Not everyone agrees that such a class should even exist. There is even less agreement on the characteristic of drugs in this class, and which specific drugs should be considered a part of this class. In addition, understanding the processes by which generic drugs are marketed and the regulations that govern how they are dispensed is important to understanding this debate. The FDA publishes its findings regarding therapeutic equivalence in the publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations. This valuable resource is commonly referred to as the Orange Book. The Orange Book should be the first reference consulted in the evaluation process of the use of a critical dose drug. It is widely available in most pharmacies as well as on the Internet.
Background

The first step in providing a framework to aid in the evaluation of the use of critical dose drugs in specific patients or patient populations is to define the key terms used in discussion of these issues. APhA, with the assistance of its expert panel, has developed the following approach to define and understand the terminology used. APhA suggests that the terminology that is currently being used in the literature does not encompass the many complex variables that require consideration when using critical dose drugs.

Critical dose drugs have most commonly been referred to as narrow therapeutic index (NTI) drugs. The term NTI became commonly used, even though the term used in FDA regulations is narrow therapeutic ratio. The FDA defines a drug with a narrow therapeutic ratio as one in which:

- There is less than a twofold difference in median lethal dose (LD<sub>50</sub>) and median effective dose (ED<sub>50</sub>) values, or
- There is less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
- Safe and effective use of the drug products requires careful titration and patient monitoring.<sup>1</sup>

The term NTI is limiting in that it implies that the only important characteristic of the drug is the ratio of the effective dose to the toxic dose. The term would seem to apply, then, only to those drugs for which specific drug levels may be measured. In addition, the term NTI fails to capture the importance of what effects the drug may have directly on the patient.

For these reasons, the term critical dose drug has come into use.<sup>2</sup> Critical dose drugs have been defined to share the following characteristics:

- Narrow therapeutic range,
- Requirements for blood level monitoring,
- Dosing based on body weight or other highly individualized dosing requirements,
- Serious clinical consequences of overdosing (toxicity) or underdosing (lack of effect), and
- Steep dose-response relationship for either efficacy or toxicity, or both.<sup>3</sup>

Drugs that have typically been described as NTI or critical dose drugs include the following: lithium, cyclosporine, warfarin, phenytoin, levothyroxine, carbamazepine, digoxin, quinidine, and theophylline. These drugs have been identified in the literature as some of the products for which the issues described in this publication exist. APhA anticipates this list to evolve as new products are developed and brought to market.

This document uses the term critical dose drugs to refer to NTI drugs generally, but it is recognized that this term alone is insufficient as a foundation for the development of the framework that is needed to effectively analyze the use of these products. The framework is built on a foundation consisting of the definitions and the interactions of three specific terms: (1) critical use drug; (2) critical dose drug; and (3) critical bioavailability drug. The Venn diagram in Figure 1 illustrates how these terms relate.

Key Terms

The analysis begins with the delineation of each situation and where it falls within the Venn diagram. Identifying the group to which a specific drug belongs must be done on a case-by-case basis. Some drug products may fall into all three categories, and others may fall into just one or two of those categories. Others may fall into different categories when used in different patients or situations. The category that a drug falls into most frequently will determine how it should be evaluated.

Learning Objectives

After reading this article, health care practitioners should be able to:

1. Define and explain key terms involving the use of critical dose drugs.
2. Examine and describe clearly the Food and Drug Administration’s standards in determining bioequivalence and therapeutic equivalence for all drugs, including critical dose drugs.
3. Explain the regulation of generic drugs with respect to both the approval process and substitution of generic equivalents.
4. Dispel concerns and misconceptions about generic substitution of critical dose drugs.
5. Provide a step-by-step framework for analyzing the use and substitution of generic equivalents of critical dose drugs in specific situations.
Critical Use Drug

The term critical use drug was created by APhA’s expert panel to aid in understanding critical dose drug issues. A critical use drug is one that is used in a patient with one or more critical variables, which may have an adverse effect on the safety or efficacy of the drug treatment (i.e., a negative patient outcome). Any drug can become a critical use drug at any time within a given patient (e.g., a patient with acute renal failure) or group of patients (e.g., neonates). With a critical use drug, the emphasis is on variable patient factors as opposed to a specific drug’s formulation or pharmacokinetic behavior. For example, patient factors that may have such effects include the specific disease state being treated; comorbid disease states; concomitant drug therapy; the patient’s age; the patient’s mental or physical condition, or both; and the patient’s ability to adhere to the drug therapy. The category of critical use drugs is the broadest of the three defined.

As is evident in the Venn diagram, all critical dose and critical bioavailability drugs fall into the critical use category. Although one could argue that all drug therapy is critical use, the term is intended to identify drugs that are being used in persons who are at increased risk (possibly transiently) for negative outcomes from their drug therapy.
One example is the case when imipenem-cilastatin (Primaxin®) is used in a patient with decreased renal function. Normally, the drug is used to treat difficult infections, and it has a relatively wide therapeutic range. However, it is renally eliminated, and with decreased kidney function, the drug can cause seizures. Thus, it becomes critical to use the drug in the correct dose and dosing interval to allow the body time to eliminate it and avoid significant toxicity.

Drugs used in the very young or very old, in persons who are critically ill, or in persons who have significant dysfunction of the liver, heart, lungs, brain, or kidneys (as already mentioned) fall into the critical use category. Every health care professional shares in determining whether a drug used in a specific patient, at a specific time, for a specific physiologic state, constitutes a critical use drug. Thus, all share the responsibility for the analysis of drugs determined to be in this category.

Critical Dose Drug

A critical dose drug is one in which a small change in dose or concentration results in a clinically significant change in efficacy or toxicity. The term critical dose drug is not sufficient for our purposes because it implies that the drug or the actual amount of drug absorbed is the most important characteristic to determine criticality. Patient-specific issues (as detailed above) also may play a significant role. This term focuses on the drug product itself—specifically formulation and pharmacokinetic factors. In other words, a critical dose drug is one for which a very precise dose must be given in order to gain the expected therapeutic effect without a toxic effect. The drugs that would most often be listed in this category are those that are routinely monitored (via blood levels).

Phenytoin is an example of a critical dose drug primarily because of its Michaelis-Menten pharmacokinetics. The nonlinear nature of phenytoin’s metabolism leads to a very steep dose-response curve. Large increases in dose may result initially in a very small change in plasma concentration. However, as the patient nears the steep portion of the dose-concentration curve, a minuscule dose increase will lead to a disproportionate increase in plasma concentration (and often toxicity). Phenytoin is also highly protein bound both to serum albumin and α1-acid glycoprotein, causing fluctuations in unbound phenytoin (i.e., that available to cause an effect) for many disease states (e.g., congestive heart failure, closed head injury, critical illness, malnutrition). Thus, phenytoin can be considered both a critical dose and a critical use drug.

Most people may not consider aspirin to be a critical dose drug. However, it falls into that category when it is used in large doses to treat rheumatoid arthritis. At such doses (up to 20 325-mg tablets per day), a small increase in dose can produce toxicity because the drug’s kinetics at that point become nonlinear. Thus, the amount of drug consumed becomes the critical factor in determining a patient’s response.

Critical Bioavailability Drug

The third term is critical bioavailability drug. Any drug that falls into this category is also a critical dose and a critical use drug. A critical bioavailability drug is one that is not consistently absorbed by the body. The variability in absorption is most often dictated by the drug’s formulation. The Sandimmune® version of cyclosporine is an example of a critical bioavailability drug. Here, the liquid and the gelatin capsules go into solution in the small intestine poorly and the chemical is unsatisfactorily absorbed through the intestinal villae. New formulations of cyclosporine (Neoral® and SangCya®) have provided a product that is much more consistently absorbed and utilized. These new formulations are no longer considered to be critical bioavailability drugs, but cyclosporine remains a critical dose and critical use drug.

A drug may be a critical bioavailability drug when administered by one route but not when administered by another route. For example, nitroglycerin when taken by mouth is destroyed by extensive first-pass metabolism and the bioavailability is quite low. However, nitroglycerin administered sublingually or intravenously is not a critical bioavailability drug because these routes of administration bypass hepatic metabolism the first time through the body.

Examples

Drugs must be categorized on a case-by-case basis because particular ones may fall into different categories depending on their use, as detailed above. For example, cyclosporine may fall into all three categories regardless of the situation in which it is used. It is a critical use drug because of the patient population in which it is used (posttransplant). It is a critical dose drug primarily because the variability in serum concentration is frequently quite large until the function of the transplanted organ is stabilized. Finally, as detailed above, when using the Sandimmune® version (primarily), it is also a critical bioavailability drug.
Evolution of the Issues

One of the precipitating events of the debate concerning substitution of critical dose drugs occurred on March 26, 1997, when the FDA approved Barr Laboratories’ abbreviated new drug application (ANDA) for warfarin sodium over the objections of Dupont Pharma, the manufacturer of the brand name drug Coumadin®. Shortly thereafter, the pharmacy literature began to focus attention on the issue of NTI drugs. Then, in April 1997, the Journal of the American Medical Association published a study claiming that generic thyroid products were bioequivalent to Knoll Pharmaceuticals’ Synthroid®. More recently (October 31, 1998), the FDA approved a therapeutically equivalent form of cyclosporine: SangCya® Oral Solution (cyclosporine oral solution, USP [modified]) manufactured by SangStat Medical Corporation. This chemical is a generic formulation of the Novartis product Neoral® Oral Solution.

These activities have led to initiatives by some brand name manufacturers of these products to attempt to distinguish them from the generic counterparts that the FDA has concluded to be therapeutically equivalent. Some brand name manufacturers have characterized these medications as a unique class of drugs that deserve special attention and more rigorous bioequivalence standards. The FDA has rejected this notion and defends its standards as being sufficient for these drugs as well as any others. In addition, some brand name manufacturers have lobbied for legislation at the state level that restricts the substitution of these types of drugs, an effort that has had minimal success.

Generic Drug Approval Process

History

The Federal Food, Drug, and Cosmetic Act (the Act), enacted in 1938, required drug manufacturers to file a New Drug Application (NDA) for each newly introduced drug. This NDA was required to establish the safety of the drug product. In 1962, the Kefauver-Harris Amendments were added to the Act. These amendments required drug manufacturers to establish that the drug product was effective for its claimed indication(s). As a result, manufacturers of any new drug (brand name or generic) marketed after 1962, were required to prove both the safety and efficacy of the product. Although an ANDA process existed at the time, it did not apply to drugs marketed after 1962, so generic versions of products approved after 1962 were still required to submit an entire NDA, including clinical trials to prove safety and efficacy.

The 1962 legislation also provided an exemption from the NDA approval process for drugs that had been marketed before 1938, as they were determined to be generally recognized as safe and effective (i.e., the grandfather provision).

Drug Price Competition and Patent Protection Term Restoration Act

In 1984, Congress passed the Drug Price Competition and Patent Protection Term Restoration Act, commonly referred to as the Waxman-Hatch Act. This legislation was a congressional effort to strike a balance between the two competing forces in the pharmaceutical industry: the generic drug firms and the innovator (pioneer or brand name) drug firms. With the passage of this legislation, generic drug firms gained greater access to the market for prescription drugs, and innovator drug firms gained certain increased periods of market protection through special patent extensions and awards of periods of market exclusivity.

Title I of the Waxman-Hatch Act extended the ANDA process to generic versions of drugs first approved and marketed after 1962. This eliminated the requirement that generic manufacturers duplicate expensive clinical and animal research to demonstrate the safety and efficacy of the drug product. Generic manufacturers were now permitted to submit ANDAs that relied on the FDA’s prior determinations of the safety and efficacy of the pioneer drug. It was recognized that the safety and effectiveness of the drug had been amply demonstrated by adequate and well-controlled studies by the pioneer drug manufacturer, by the acceptance of these findings by the medical community, and by the widespread use of these drug entities in patient therapy over many years.

Title II of the Waxman-Hatch Act compensated the pioneer companies for losses due to competition from the generic companies by extending the patent terms of some pioneer drugs.

New Drug Application versus Abbreviated New Drug Application. To submit an ANDA for a gener
drug, there must be a previously approved drug that is the same as the proposed drug. A generic firm must submit information to show that the product provided in the ANDA is the same as the previously approved brand name drug in terms of active ingredient, dosage form, strength, and route of administration. Additionally, all generic manufacturers must comply with the same precise and very stringent FDA requirements imposed on the brand name products. They must meet the same standards for manufacturing practices, identity, strength, quality, and purity. Minor differences in labeling are allowed to account for patent exclusivity protection or manufacturer-specific modifications such as tablet shape, color, and so forth.

Figure 2 illustrates that the only difference in requirements for an NDA and an ANDA is that the ANDA does not require evidence of safety and efficacy.

Role of the Orange Book

The Orange Book is the authoritative source on the therapeutic equivalence of FDA-approved products. It is a comprehensive source on all drug products with approved NDAs or ANDAs. Therefore, any drug product that is contained in the Orange Book has been fully reviewed and approved for safety and efficacy by the FDA.7

In determining therapeutic equivalence, the FDA procedure compares one generic formulation with the reference or innovator formulation. This product is referred to as the reference listed drug. A reference listed drug is defined in FDA regulations as the “listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.”8 By designating a single reference listed drug as the standard to which all generic versions must be bioequivalent, the FDA hopes to avoid possible significant variations among generic drugs and their brand name counterparts. Such variations could result if generic drugs were compared with different reference listed drugs.

There may be an instance when multiple NDAs are approved for a single drug product, and a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug is actually shielded from generic competition. The FDA has a process that allows a firm wanting to market a generic version of such a drug to do so. Through this process, the product with the NDA becomes an additional reference listed drug. Therefore, in some situations there may be more than one reference listed drug.

Orange Book Ratings. The therapeutic ratings contained in the Orange Book are typically in a two-letter format. The first letter tells whether the product is therapeutically equivalent, and the second letter provides additional information on the basis of FDA’s evaluation.

The ratings can be divided into three categories: A, AB, and B. Drugs given an A rating have no known or suspected bioequivalence problems and are considered to be therapeutically equivalent to other pharmaceutically equivalent products. Those drugs given an AB rating are those for which actual or potential bioequiva-
lence problems have been resolved with adequate bioequivalence testing. Those that are not considered therapeutically equivalent are given a B rating.

When there are two or more reference listed drugs, the rating will be three digits. The number added on the end indicates to which reference listed drug the generic is determined to be equivalent (e.g., AB1 or AB2).

Grandfathered Drugs and the Orange Book. Some drugs that were marketed before 1938 were initially exempt from the NDA process. The FDA has taken the position that any new dosage form of these chemicals constitutes a new drug. Therefore, it requires the same information that would be required of more recently approved drugs. It is a common misconception that all drugs marketed before 1938 are excluded from the Orange Book. Examples of drugs marketed before 1938 include quinidine, theophylline, phenytoin, digoxin, and levothyroxine. Quinidine, theophylline, and phenytoin are included in the Orange Book, which means that they have gone through the FDA approval process (NDA or ANDA) and have bioequivalence data.9

Understanding FDA Therapeutic Equivalence

Under the Waxman-Hatch Act, the FDA considers drug products to be therapeutically equivalent if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients for the approved indications of use.9 Specifically, the FDA considers a drug to be therapeutically equivalent (and therefore substitutable) if it meets all the following criteria:

1. It is pharmaceutically equivalent.
   a. It contains the same amount of active drug in the same dosage form.
   b. It meets compendial standards for purity, strength, identity, and quality.
2. It is bioequivalent.
3. It is adequately labeled.
4. It is manufactured in compliance with Good Manufacturing Practice regulations.7

In other words, the generic product must pass all the same tests and have all the same qualities of the name brand product, in addition to being bioequivalent.

Bioequivalence

The Waxman-Hatch Act requires that a generic product be proven to be bioequivalent to the pioneer drug before it is deemed to be therapeutically equivalent and, therefore, interchangeable. The FDA’s standards for bioequivalence have been widely misinterpreted and misrepresented. This may be due to the fact that the requirements are quite complex and involve statistical calculations.

The concept of bioequivalence is based on the relationship between the time course and concentration achieved in blood after a dose of a drug and its expected clinical effect. Generally, under the Federal Food, Drug, and Cosmetic Act, a drug is considered to be bioequivalent to another drug if the rate and extent of absorption of the generic drug are not significantly different from the rate and extent of absorption of the brand name drug when administered at the same dose under similar circumstances.10 This is generally proven through the completion of a bioequivalence study, although in some instances more extensive testing may be required. A bioequivalence study is ordinarily conducted with 18 to 36 human volunteers. With a systemically absorbed drug, blood levels (even from the same product) may vary in different subjects. Therefore, in a typical study, each subject receives both the innovator and the test drug products in a randomized crossover design, and as a result, serves as his or her own control. Single doses of the test and reference drugs are administered, and blood or plasma levels of the drug are measured over time.

Calculating FDA Bioequivalence. The FDA then requires bioequivalence to be calculated using three pharmacokinetic parameters: the maximum concentration ($C_{\text{max}}$), the time at which the maximum concentration is reached ($T_{\text{max}}$ also known as $T_{\text{peak}}$), and the area under the curve (AUC). The rate of absorption is evaluated by measuring the $C_{\text{max}}$ and the $T_{\text{max}}$. The extent of absorption (the amount of drug absorbed) is calculated by measuring the AUC. The innovator’s product is the reference standard for AUC, $C_{\text{max}}$, and $T_{\text{max}}$. To be considered bioequivalent, a generic drug must demonstrate that its values for AUC, $C_{\text{max}}$, and $T_{\text{max}}$ are similar to those of the innovator’s product (see Figure 3).

The calculations used to determine the similarity in these pharmacokinetic parameters measuring the rate and extent of absorption involve rather complex statistics. To be precise, the calculation requires that the 90% confidence interval for the ratio of the mean response (usually $C_{\text{max}}$ [rate] and AUC [extent]) of the generic drug fall within 80% to 125% of that of the brand name drug, using log-transformed data. Practically, this confidence interval calculation shows that nine times out of ten, the mean response of an individual (when tested in precisely the same way) would fall within the same numerical limits of the original
test. Alternatively, there is only a 10% chance that an individual would have a mean response outside the limits of the original test.

This rule often is misinterpreted or misrepresented as meaning that the mean bioavailability (rather than the 90% confidence interval of the mean response) of the generic drug must be within 80% and 125% of that of the reference product. Because the computation of a confidence interval is influenced by the study design—considering the number of subjects and the intrasubject variability inherent in the bioequivalence testing—the actual differences in AUC or Cmax between test and reference products must be considerably less than -20% to +25%. In fact, if the true difference is near -20% or +25%, one or both confidence intervals are likely to fall outside the acceptable range and fail the bioequivalence test (see Figure 4).

The actual differences in AUC or Cmax usually vary by less than 5%. In fact, the first 224 post-1962 drugs approved over the 2-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%.11

Individual Bioequivalence—Considering a New Approach. One criticism of the current system is that it fails to take into account, or to test for, differences in bioavailability of a drug used in certain subsets of a population. For this and other reasons, the FDA is in the process of considering a new approach to documenting bioequivalence. This approach is termed individual bioequivalence. It allows the possibility of scaling the bioequivalence “goalposts” (i.e., the boundary of 80%-125%) based on variability of the reference listed

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**Figure 3.**

Pharmacokinetic Basics: Maximum Concentration (Cmax), Time at Which Maximum Concentration Is Reached (Tmax), and Area Under the Curve (AUC) for an Innovator and a Generic Drug

Although the AUCs (amounts absorbed) are comparable, the absorption rates (Cmax and Tmax) are quite different; thus, these two products would not be considered bioequivalent under FDA standards.
Figure 4.

Bioequivalence Cases

Case I: Test Product Shown to Be Bioequivalent

Case II: Test Product Not Shown to Be Bioequivalent

TEST PRODUCT LOW

Case III: Test Product Not Shown to Be Bioequivalent

TEST PRODUCT HIGH

Case IV: Comparison of Two Bioequivalent Generic Products

Case V: Test Product Bioequivalent
drug. One possibility is that for critical dose drugs, the goalposts would always be scaled to the variability of the reference listed drug. This may have the effect of narrowing or even widening the goalposts in a given instance. For example, a reference drug with a wide variability (e.g., Sandimmune®) would have wider goalposts (i.e., >80%–125%) than a drug with less variability (which may continue to have the 80%–125% range or less).

**No Therapeutic Differences Seen**

What is certainly as significant as the material described above is that no serious therapeutic differences between brand name innovators and FDA-approved generic drugs have been reported. The FDA has stated that no clinical data have been submitted to the agency that would warrant narrowing the present 90% confidence interval of mean response for any drug or class of drugs. In fact, in a recent article citing opinions of transplant pharmacists in which the majority believed the FDA’s current bioequivalence standards were inappropriate for critical dose drugs, none of the pharmacists whose transplant centers used generic drugs reported that their patients had any clinical problems as a result.

It is reasonable to assume that if any brand name manufacturer had evidence of any clinical or therapeutic variability between its product and a generic one, it would report those findings to the FDA. The bottom line is that there is no evidence that the FDA’s current bioequivalence standards are inadequate to ensure the clinical and therapeutic efficacy of generic critical dose products.

**Regulation of Generic Substitution**

The next step in understanding this issue focuses on the regulation of generic substitution in the dispensing process. The process of generic drug approval, as just discussed, is regulated at the federal level by Congress and the FDA. The actual prescribing and dispensing of medication constitute the practice of medicine and pharmacy, respectively, and are regulated at the state level by the states’ medical and pharmacy boards.

**Product Selection Laws**

In the early 1970s many states still had in effect antisubstitution laws that prohibited pharmacists from dispensing a generic drug for a brand name product. Many of the laws had been passed 25 years earlier to control the distribution of substandard counterfeit drugs. However, in 1975, the Department of Health and Human Services implemented the concept of maximum allowable costs for the reimbursement of selected generic drugs covered by the Medicaid program. Through this program, states with antisubstitution laws could not participate in the Medicaid prescription drug program because the cost for the innovator’s brand name product was almost always higher than the maximum allowable cost. Therefore, in the mid-1970s states began repealing their antisubstitution laws and replacing them with product selection laws that became applicable to all prescriptions. The basis for these laws was the Model Drug Product Selection Act that was prepared by the Federal Trade Commission (FTC).
As a result, today, every state has some type of product selection law. Some states use negative formularies, and some use positive formularies. Some laws are mandatory, and others are permissive. In mandatory states, pharmacists must substitute a less expensive generic drug for the brand name unless the prescriber indicates otherwise, as required by the law. In permissive states, a pharmacist may choose to substitute if the prescriber issues the prescription in a way that permits substitution. Generally, the product selection rules apply only when a specific product has been prescribed, usually through the use of a brand name. If a prescription is written generically, the pharmacist may dispense any product containing the prescribed drug pursuant to a generically written prescription subject to good professional judgment.

Although these laws vary from state to state, they all have one common feature—that is, the prescriber retains the prerogative to limit or prohibit drug product selection. The method by which the prescriber may prohibit selection varies from state to state. For example, some states require the physician to make a notation on the prescription such as DAW (dispense as written) or DNS (do not substitute). Other states may require the prescription to have two signature lines—one allowing substitution, the other prohibiting it. The NABP Survey of Pharmacy Law contains a table summarizing the major components of the various states’ product selection laws and related examples as to how they are similar and differ from one another.

At least 16 states have adopted the FDA’s Orange Book as the authority (i.e., formulary) regarding what generic products may be substituted.

**Specific Legislative Initiatives on Narrow Therapeutic Index Drugs**

During the past few years, as this issue of critical dose drugs has manifested, some brand name manufacturers have made legislative initiatives at the state level pertaining to NTI drugs. During 1997–1998, at least 32 states had some sort of legislation introduced or other activity by lobbyists for brand name manufacturers to restrict access to generic NTI drugs. To date, however, such legislation has passed in only three states: Texas, Virginia, and North Carolina. Generally, this legislation is a supplement to the states’ product selection laws. Usually, the legislation defines an NTI drug and sometimes lists specific drugs that are considered NTI drugs. Typically, the legislation prohibits pharmacists from refilling a prescription for an NTI drug with one made by a different manufacturer unless they obtain documented consent from both the patient and the prescriber.

Of the three states that have passed this legislation, only one (North Carolina) has taken initiatives to enforce it. In Virginia, the state board of pharmacy, based on an attorney general’s opinion, has determined that the state’s current product substitution law (which consists of a check box system on the prescription form) is sufficient for a prescriber to authorize or prohibit substitution of NTI drugs. The board voted not to require any further permission from the prescriber. In Texas, the implementation of the statute has been held up by litigation contesting the process by which the implementing regulations were adopted.

**Potential for Pharmacist Liability**

In the 1970s, when states’ antisubstitution laws were being replaced with drug product selection laws, some were concerned that pharmacists may incur greater liability risks for engaging in drug product selection. The FTC’s Model Drug Product Selection Act contained a provision designed to limit a pharmacist’s civil liability when substituting a generically equivalent drug in place of the brand name product. It stated:

Any pharmacist who selects an equivalent drug pursuant to this section incurs no greater liability in filling the prescription by dispensing the equivalent drug product than would be incurred in filling the prescription by dispensing the brand name drug prescribed.

Most states today have the same type of provision contained in their product selection laws. The effect of such a provision is that if pharmacists comply with their state’s product selection laws, they may incur no greater liability than if they had dispensed the name brand drug product. These provisions do not differentiate between critical dose drugs and other drugs.

With the passage of over two decades, such liability simply has not resulted. The potential that a pharmacist could be held liable for his or her role in product selection is more theoretical than actual. "Nowhere in the U.S. has a pharmacist incurred additional liability for dispensing a generic drug product in
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accordance with a state’s generic drug substitution laws. In fact, one study shows that just under 1% of all claims against pharmacists involve generic interchange issues.

Some of the literature on the topic of critical dose drugs has suggested that a pharmacist’s potential liability in the drug product selection process is greater when a critical dose drug is substituted than when other types of drugs are substituted. As in the instance of bioequivalence, an attempt is made to distinguish the substitution of critical dose drugs from the substitution of other types of drugs. There are no reported cases of pharmacist’s liability for harm alleged to have occurred due to the legal substitution of a generic product for a prescribed trade name product. This potential liability has been overstated.

It is often cited that NTI, or critical dose, drugs are involved in many claims against pharmacists. In addition, a trend that shows a rise in pharmacy malpractice claims and higher verdicts and settlements is detailed. However, this trend has nothing to do with the generic substitution of critical dose drugs. It is that critical dose drugs, by their very nature, are more likely to be involved with liability suits, regardless of whether they are substituted with generic equivalents or not.

The probable reason that there have not been any malpractice cases involving the legal substitution of a generic product, and the reason it is unlikely that there will be any of these cases in the future, is that this type of case is very difficult for a plaintiff to prove. The plaintiff would have to prove that his or her injury was “more likely than not” the result of the pharmacist’s election to dispense an exact generic equivalent product rather than the brand name product ordered by the prescriber. For example, the patient would have to prove that the dispensed product was different in some way from the prescribed product. That difference then would have to be proven to be the proximate (legal) cause of the harm that resulted.

One case that demonstrates this concept is LeJeune v Trend Services (Slip Op 96-550, June 4, 1997; 1997 La App Lexis 1541). The plaintiff in the case was given generic medications instead of the brands prescribed because the insurance provider which paid for the medications determined that generics should be substituted. The patient was not told by his physician, pharmacist, or employer (who paid for the prescription benefit program) that the insurance company would pay for the prescribed name brand if the physician indicated “dispense as written” on the prescription. The patient claimed that by being forced to take the generics, the defendants withheld prescribed treatment. Although the court agreed in principle with the plaintiff (because no one informed the patient about his therapeutic options), it held in favor of the defendants because the patient could not show that he suffered any damages.

In another case, Ullman v Grant, the plaintiff had an adverse reaction to a product that was substituted for the drug that had been prescribed. The pharmacist was found not to be liable because the court assumed that the prescribed product would have caused the same reaction. In Santiago v Barre National, Inc., although the defendant pharmacist had to settle because he failed to include a warning with a dispensed generic product, the court found that it was not the substitution of a different product that caused the harm because the originally prescribed product contained the same active drug.

As long as generic products continue to perform clinically as well as their brand name counterparts, the potential that a pharmacist’s liability may be increased for substituting AB-rated generic versions of critical dose drugs is virtually nonexistent.

Decision Analysis Algorithm

To help health care professionals more fully understand and use the information already presented, a decision algorithm has been created. This decision algorithm consists of a series of statements or questions that lead a person through the major parts of the decision-making process (see Figure 5). The following sections explain the algorithm. In addition, after the explanatory text, three decision-making scenarios have been created to illustrate use of the algorithm.

Box 1

The medication under consideration for use is new and has recently been approved for marketing. The first step in the decision process is to compare this medication with currently available therapies. This evaluation consists of evaluating it for safety, efficacy, and cost.

Proponents of brand name critical dose drugs claim that the difference in price between brand and generics is “very, very small... for warfarin, the difference is less than $2 per prescription.” Although $2 per pre-
scription may not sound like a lot of money, for patients receiving multiple therapies for extended periods of times (the rest of their lives), $2 per prescription could add up to thousands of dollars over a few years' time. This is particularly important for patients whose insurance coverage has a maximum benefit (cap). Using equally effective but less costly agents allows patients to be covered for the maximum length of time. From the perspective of the payer, lower costs for medications may allow for more money to be available to fund other programs.

Box 2

Is the new product rated A or AB in the Orange Book? If it is, then it is bioequivalent to the brand name product and can be safely and effectively substituted. If it is not, do not use this compound until it receives an A or AB rating.

Boxes 3 and 4

Is this new agent a critical dose drug? (The material in the preceding text can be used to determine whether this drug meets the criteria for a critical use, critical dose, or critical bioavailability drug.) If it is not, leave this decision algorithm and evaluate the medication based on other merits. If it is, proceed to box 5.

Box 5

Does the patient's current therapy consist of this medication, and will that therapy be converted to the alternate brand? If the answer is no, then the prescriber is initiating this medication therapy. In that case, the new therapy should be initiated and monitored as clinically appropriate. This situation is referred to as prescribability. If the answer to the above question is yes, then patients will be converted (switched) to the new therapy from existing medication. This situation is referred to as switchability.

Prescribability refers to the situation where a patient is initially being prescribed a critical dose or critical bioavailability drug, whereas switchability refers to the situation where a patient has been stabilized on a particular critical dose drug and is then switched to another brand of the same drug.

Box 6

The analysis for prescribability is performed by examining how the prescription is written pursuant to a state's product selection law and the prescriber's intent. Under a state's product selection law, the prescriber has the option to specify the brand name or generic name when the prescription is written. The prescriber needs to be aware of the specific regulations in the state in which he or she is prescribing. There are three ways for the prescription to be written: (1) the prescriber specifies the brand name product with a notation indicating that the brand name drug is to be dispensed; (2) the prescriber specifies a brand name without a notation or other indication that a brand named drug is to be dispensed; and (3) the prescriber indicates only the generic name of the drug.

In the first case, the generic drug would not be prescribable. In other words, the brand name drug would be dispensed to the patient. Most state product selection laws prohibit the substitution of a branded product if the patient makes a specific request (and of course, is willing to pay for it!). In that case, the generic drug would not be considered prescribable either.

In the second case, the applicable state's product selection law should be followed. For example, if the pharmacist resides in a mandatory substitution state, he or she would dispense a lower-priced generic drug that was deemed substitutable under the state's law. However, if the pharmacist is in a permissive state, he or she will have to consider some other factors. These factors include the patient's needs or desires; the therapeutic equivalence or nonequivalence of the generic drug; and safety, efficacy, and cost issues. Cost issues include whether the patient's insurance covers the brand name or the generic product. In addition, the pharmacist should consider his or her ability to maintain an adequate supply of whichever manufacturer's drug is dispensed in order to maintain the consistency of the patient's drug therapy.

In the third case, the state's product selection law need not be considered. However, the same factors that apply in the second case above (i.e., cost, safety, efficacy, therapeutic equivalence) would be considered.

In today's health care environment, cost always must be considered—either in terms of the patient's insurer or the patient's ability to pay. Generic drugs cost less than brand name drugs. However, it is also important to remember that the cost of drug therapy include costs other than the price of the drug product itself.

Box 7

The patient will be switched to the new therapy. The analysis of the switchability of a critical dose or critical bioavailability drug revolves around whether one
formulation may be substituted for another without concern for reduced effectiveness or increased incidence of adverse effects. Theoretically, a switch actually could be involved when a patient receives a different lot of the same manufacturer’s drug. However, most health care practitioners would not be aware of this situation.

There are two parts to consider in the analysis of switching. The first is the legality of performing the switch. The second is the issue of clinical problems resulting from the switch. Attempting to evaluate the potential for problems in an individual patient is difficult at best. The FDA bioequivalence tests state that the mean response to an A- or AB-rated drug will fall within predictable (and clinically acceptable) limits 90% of the time. If this does not happen, go to box 10.

The issue of switchability is more complex clinically and requires more analysis than the situation involving prescribability. The first question involves whether such a switch is allowed under the applicable state’s product selection law. The original prescription should be reviewed to see whether the product selection law allows for the substitution of the generic drug. If it is not allowed, the patient should be maintained on current therapy. If the patient desires a switch, however, the prescriber should be contacted to obtain his or her consent for the switch.

**Box 8**

At this stage, therapy with the new critical dose drug is initiated after notifying all affected parties. If a switch is made, it is important that all parties be informed by the person responsible for making the switch. The prescriber should be told that a switch occurred. In addition, the patient and his or her caretaker should be advised that the appearance and name of the medication may have changed. The patient also should be advised to notify his or her health care provider if he or she notices any changes in clinical effect. In the transplant environment, the transplant coordinator should be informed that such a change in therapy has been made. (Note: Although this notification would be helpful in all situations with all medication switches, it is only truly practical when dealing with critical dose drugs. For instance, a pharmacist would not even think about contacting a prescriber when switching a patient from one generic penicillin to another, or from one diuretic to another.)

The new therapy should be monitored as clinically indicated. Monitoring is a component of the cost of drug therapy. Some brand name manufacturers suggest that when critical dose therapy is switched, increased monitoring is automatically required; therefore, the cost benefits of switching to the less expensive drug are outweighed by the increased costs in monitoring. Typically, patients taking critical dose drugs require close monitoring regardless of whether or not one of their drug therapies is switched to a generic brand.

The FDA takes the position that no additional clinical tests or examinations are needed when a generic drug product is substituted for the brand name product if they are determined to be therapeutically equivalent. This statement is based on the assumption that all patients receiving these types of drugs are closely monitored anyway. “Usually these drugs [those which small changes in dose or blood level concentration may result in clinically important changes in drug efficacy or safety] require frequent adjustments in the dose of the drug and careful patient monitoring irrespective of whether the drug is a brand or generic drug product.”

**Boxes 9–11**

Is the new agent working? If the answer is yes, continue the new therapy (ensuring that the same manufacturer’s product is dispensed every time). If the answer is no, evaluate the dose, patient adherence, toxicities, and so forth. Consider switching back to the previous therapy if the patient is not tolerating the switch.

It is best to avoid multiple switches, however, as medication inconsistency does not allow the patient to receive the maximum benefit from the prescribed therapy. Multiple switching is the term used to describe the situation that can happen when there are multisource products of a certain critical dose drug. Multiple switching occurs when the patient does not consistently receive the product made by the same manufacturer. As a general rule, it is recommended that multiple switching, even among AB-rated products, should not be done in situations involving critical dose drugs.

Although the potential for multiple switching exists, at the present time it is not much of an issue. The reason is that most of the drugs that are considered critical dose presently do not have multiple suppliers. However, this issue has the potential to become more important as more manufacturers enter this market.

**Scenarios**

The following examples illustrate how to use the decision algorithm. The first is from the viewpoint of a
Figure 5.

Decision Algorithm for Substituting Critical Dose Drugs

1. The chemical under consideration is a new product. Compare with current agents in the class.

2. Is it rated “A” or “AB”? NO: Do not use this agent.

3. Is this new agent a critical dose drug? NO: Leave this algorithm and evaluate the drug on other merits.

4. YES: Leave this algorithm and evaluate the drug on other merits.

5. Will patient be converted to this new agent? NO: Patient will only be prescribed this new agent. Initiate therapy and monitor outcomes.

6. YES: Patient will only be prescribed this new agent. Initiate therapy and monitor outcomes.

7. Patient therapy will be switched to the new drug.


9. Is the new agent working? NO: Evaluate the dose, patient adherence, toxicities, etc. Consider switching back to previous therapy if patient is not tolerating the switch.

10. YES: Evaluate the dose, patient adherence, toxicities, etc. Consider switching back to previous therapy if patient is not tolerating the switch.

11. Continue routine patient monitoring.
prescriber, the second from a dispensing pharmacist, and the third from a large insurance provider.

Scenario 1: The Prescriber. M.B. is faced with a dilemma. An NTI medication that she frequently prescribes is now available from another manufacturer. She is detailed by representatives from both manufacturers and provided with marketing literature. The literature is confusing, but the new medication is 20% less expensive on a per tablet basis. Should she prescribe the drug?

M.B. remembers the decision algorithm on critical dose drug decision making. She pulls it out and walks through it. The first question is one of FDA equivalence rating. She calls a pharmacist friend, who tells M.B. that the new drug is AB rated.

By performing a literature search using Medline, M.B. discovers that a small number of randomized, controlled trials have been performed with the drug in question in the same population that she treats. She notes that the adverse effect profiles of the two medications are not significantly different. To date, however, there is no information on how to convert patients to the new form of the medication.

She decides to call the company and talk directly with the physician overseeing the trials. The company sends her the material that she needs, and she decides to cautiously try this new agent in some of her most stable and willing patients.

M.B. writes a specific prescription with the new drug name (not just a generic name) and specifies the manufacturer. To ensure that the correct product is dispensed, she talks with the pharmacist about the new medication and its merits and about how important it is for the evaluation of efficacy that the new medication be dispensed every time. The pharmacist documents this information in the patient record and highlights the new brand to be dispensed each time.

Scenario 2: The Dispensing Pharmacist. T.R. has been a pharmacist for many years. Each year it gets more and more difficult to perform the basics of dispensing—particularly with so many generic versions of drugs available and all the insurance company formularies.

Today T.R. is presented with a prescription for a new medication. She has never dispensed it before, so she consults her references. She finds that it is a competitor product to the critical dose medication that the patient is currently taking. She is pleased to note that her wholesaler stocks it. She is amazed by the cost difference between the two products. T.R. asks the patient if the prescriber told him he was going to use a new medicine. The patient says he does not remember. When asked if he wants the new medicine the patient asks, "How can I be sure it's going to work like the medicine I'm taking?! Those 'genetic drugs' have had some real problems, haven't they?"

T.R. does not quite know where to start, but she remembers that the pharmacy recently received a mailing on critical dose drug decision making. She consults that decision algorithm as a quick reference.

T.R. tells the patient that the drug has been AB rated by the FDA, which means that it is equivalent in terms of safety and efficacy to the medicine that the patient currently takes. Also, she tells him that all drugs, generic or not, are manufactured under the same stringent conditions. The patient says, "Well, I'm still not sure. See what my doctor says." She tells the patient that she will ask his doctor whether he truly wanted to switch medications. She asks whether he can wait, or whether he would like his regular medication right away. For the cost difference, he says he will wait.

The phone call to the prescriber confirmed that he wants to try this new medication and that he is comfortable with the science behind it. He is pleased to know that it will reduce the patient's cost as well. T.R. asks the prescriber when the patient will require a return to the office for a checkup. He tells her not for 6 months.

Scenario 3: The Large Insurance Provider. M.L., a vice president of health care services, is working at his desk. One of his employees tells him that there is a new critical bioavailability medication available generically to treat 100,000 of his covered patients. The drug is AB rated according to the Orange Book on the Internet. Its price is significantly less than that of the name brand. How should M.L. go about making the decision as to whether the company should pay for the generic product?

M.L. decides to forward the question to his formulary committee. He also forwards a copy of a publication on critical dose drug decision making to them. The committee reviews the literature as well as the decision algorithm. It also listens to presentations from both manufacturers. After this thorough review, the committee members decide that not enough studies have been conducted in the target population to warrant a wholesale switch. However, because the product is AB rated, they approve the new product’s use as a formulary item and decide to gather and analyze the usage data. They ask both companies to return in 6 months or when significant new data are published.
Summary

The issues surrounding the generic substitution of critical dose drugs will continue as long as drug manufacturers continue to exist and compete. The consistency of the definitions of the key terms used in discussion of this issue is of the utmost importance. The process by which drugs are approved and come to market in the United States ensures that safe, effective, and less expensive drug therapy is available for those patients who need it. The FDA carefully oversees the complex calculations used in determining the therapeutic equivalence of all drugs—including those that are considered to be critical dose drugs. The method currently used to determine the bioequivalence of generic drugs is the same method required of brand name manufacturers to determine the bioequivalence of subsequent formulations of their own products. There is no reported clinical or therapeutic difference between generic forms of critical dose drugs and their brand name counterparts with respect to efficacy or side effect profile. In addition, to date, pharmacists have not incurred additional liability for dispensing generic counterparts of brand name products. When the substitution of a critical dose drug is made, it is prudent to notify all affected parties.

The FDA’s publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) is a valuable source of information for health care professionals who deal with these issues. Although regulation of the substitution of generic drugs has been the subject of local legislative efforts, in all but one state the same rules govern the substitution of both critical dose drugs and all other types of drug products. Use of a decision analysis tool such as the algorithm provided in this monograph should lead to efficient review of any new compound. The primary decision points in the analysis process are the safety and efficacy of the generic product compared with the innovator compound, the relative cost differential, whether the patient is being switched or prescribed the therapy for the first time, how the switch is conducted, and monitoring for continued safety and efficacy.

With these issues in mind, all new critical dose medications can be rapidly evaluated and patients can receive the highest level of care at the most efficient cost.

References

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