

## SPECIAL REPORT

# Drug Substitution in Transplantation: A National Kidney Foundation White Paper

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• Specific safeguards to guide the approval process and substitution practices for generic immunosuppressive agents are necessary for the effective delivery of patient care. Currently, the Food and Drug Administration (FDA) requires the demonstration of bioequivalence of generic drugs to innovator drugs in normal healthy subjects, a criterion that may be insufficient for critical-dose drugs. For generic equivalents of critical-dose drugs and for innovator critical-dose drugs, there should be a requirement for replicate studies measuring intrasubject variability and subject-treatment interactions to establish that bioequivalence holds true. Extensive testing of generic drugs in all target patient types is impractical and should not be required. However, when evidence suggests that the bioavailability of a critical-dose drug may vary substantially in certain subgroups, the FDA should require a demonstration of bioequivalence of generic versions to innovator products in these representative target populations. Changes in the approval process for generics should be accompanied by more consistent substitution practices. Pharmacists should notify the prescribing physician and patient whenever a critical-dose drug (generic or brand name) is dispensed in a different formulation from the one the patient has been taking. Therapeutic substitution for such drugs should not be made unless the prescribing physician has granted approval. The health care provider should consider instituting appropriate monitoring whenever patients are switched between generic formulations or between innovator drugs and generic formulations. Patients should be well informed about generic substitutes so that they can participate in treatment choices.

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**INDEX WORDS:** Transplantation; immunosuppressants; bioequivalence; bioavailability; switchability; generics.

**T**HE NATIONAL Kidney Foundation (NKF) has a well-established history of serving as a neutral catalyst for the discussion of current issues and medical problems that directly affect patient outcomes and delivery of patient care. A conference on “Drug Substitution in Transplantation” (April 1998) was organized by the NKF to review the recent literature and to develop recommendations for the safe and effective use of generic immunosuppressant drugs in solid organ–transplant recipients.

Conference participants represented various disciplines involved in transplantation: surgeons, physicians, pharmacists, nurses, transplant coordinators, social workers, health economists, and patients. Pharmacokinetic, therapeutic, ethical, and economic issues involved in immunosuppressant drug substitution were explored to develop recommendations that would best serve individual patients within the realities of today’s health care system.

### RATIONALE FOR THE MEETING

Generic substitution is a key issue in transplantation because transplant drugs are expensive, and the consequences of poorly controlled immunosuppression (ie, graft rejection or drug-

induced toxicity) are serious. The participants deemed it important to make recommendations about generic substitution because of concerns expressed in the transplant community that the current bioequivalence requirements for generic drugs are insufficient for assessing immunosuppressive transplant drugs. This is a particularly timely issue, because several generic immunosuppressive agents are likely to become available in the near future. Although the patents for trans-

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*Conference participants were a multidisciplinary group, including transplant recipients, and represented leading transplant programs (all solid organs) and others from around the United States. Presenters and participants were selected on the basis of expertise and professional background.*

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plant drugs such as prednisone, azathioprine, mycophenolic acid, and rapamycin expired several years ago, the patent for cyclosporine expired in 1995, and generics will be available in the near future. In addition, the patents for tacrolimus and mycophenolate mofetil will expire in 2002 or later. Therefore, updated guidelines should be in place as these new generics undergo review.

To address this topic knowledgeably, the participants reviewed key terms, the history of drug substitution, the evolution of bioequivalence testing, and historical perspectives on bioequivalence. The key points of this review are summarized here.

## BACKGROUND

### *Terminology*

*Average bioequivalence* compares the population averages of bioavailability for test (usually the generic) and reference (usually the brand-name) products. Average bioequivalence does not compare variances or distribution of bioavailability in the test and reference products. Therefore, it would be possible, for example, for two formulations with very different bioavailabilities to be found bioequivalent as defined by average bioequivalence criteria.<sup>1,2</sup>

*Bioavailability* refers to the rate and extent to which the active ingredients or moieties are absorbed from a drug product and become available at the site of action. For systemically active drugs, measurements of blood concentrations are usually used. For drugs for which the availability at the site cannot be directly measured, biological effects may be measured instead.<sup>3</sup>

*Bioequivalence* refers to comparable bioavailability of a drug product to a pharmaceutically equivalent innovator or appropriate reference drug product examined under appropriate experimental conditions.<sup>3</sup>

*Critical-dose drug* (discussed later)

*Individual bioequivalence* compares the bioavailability of test and reference product in a manner that includes assessment of the variability in bioavailability in the individual over time (intrasubject variability) as well as the subject-

by-formulation interaction. Individual bioequivalence is the relevant criterion for a patient being switched from one formulation to another.<sup>1,2</sup>

*Narrow therapeutic range drug* is a drug for which small changes in systemic concentrations can lead to marked changes in pharmacodynamic response.<sup>4</sup> The Food and Drug Administration (FDA) points out that the narrow therapeutic index designation is not a formal designation by the FDA; however, *narrow therapeutic ratio* as a term is defined in the FDA regulations.<sup>5</sup>

*Pharmaceutical equivalents* are drugs that contain the same active ingredient in the same strength (concentration) and dosage form and are intended for the same route of administration.<sup>3</sup>

*Population bioequivalence* compares test and reference product bioavailability by assessing the similarity of means of their distributions. This form of bioequivalence is the relevant criterion for a patient being started on a new drug.<sup>1,2</sup>

*Prescribability* is the willingness to prescribe a drug to a patient for the first time because confidence in the drug's efficacy and safety have been assured by population bioequivalence.<sup>1,2</sup>

*Subject-by-formulation interaction* is a term that identifies significant differences in the individual bioavailabilities of the test and reference products in a subset of the tested population.<sup>1</sup>

*Switchability* is the ability to appropriately transfer a patient from one formulation of the drug product to another (high confidence in switchability is assured by individual bioequivalence).<sup>1,2</sup>

*Therapeutic equivalence* of two drug products requires pharmaceutical equivalence, bioequivalence, and several other characteristics, including in vitro quality control. Therapeutic equivalence is not defined by a measured clinical effect.<sup>3</sup>

### *Historical Perspectives on Drug Substitution*

The regulations for generic drugs have changed during the course of pharmaceutical history. The Food, Drug, and Cosmetic Act was enacted in

1938 to promote the safety of new drugs. This act required the submission of a new drug application for all new drugs, including generics. Under the Kefauver-Harris Amendment of 1962, proof of a drug's efficacy and safety for its intended use was required before approval. This legislation required that randomized, well-controlled clinical trials be conducted for approval of new brand-name and generic drugs.<sup>6</sup> In 1968, the FDA, working through the Drug Efficacy Study Implementation, invited generic drug manufacturers seeking product approval to submit abbreviated new drug applications requiring safety and efficacy data, information about the manufacturing process, and demonstration of bioequivalence to the brand-name product.<sup>7</sup> Because generics were required to meet essential safety, efficacy, and bioequivalence criteria, few were approved under these regulations. In 1984, the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act) permitted the FDA to approve generic products for drugs that had already been found safe and effective and formalized the criteria for pharmaceutical equivalence and bioequivalence. Under this act, the period of patent protection was extended to 20 years to encourage new drug development, and the approval process for generic drugs was simplified. It eliminated the requirement for randomized trials to demonstrate clinical efficacy as long as bioequivalence was shown and no bioequivalence problems were known or suspected. Many more generics became available after this act simplified the requirements for approval.

Metrics (standardized measurements) for determining bioequivalence evolved as the legislation was implemented. No specific bioequivalence testing was required for generic drugs before the DESI requirements. Initially, the DESI required demonstration of bioequivalence of generics to innovators through *in vitro* comparisons of dissolution characteristics or through comparative *in vivo* data.<sup>7</sup> In 1977, a pharmacokinetic measurement of bioequivalence was established by The Bioavailability and Bioequivalence Regulation of the FDA. This metric focused on mean values for extent (area under the plasma concentration–time curve, AUC) and rate (peak plasma concentration,  $C_{\max}$ ) of absorption. It allowed a claim of bioequivalence when the null hypothesis of similarity for means of AUC and  $C_{\max}$  was not

rejected at the 95% significance level. The test was powered so that a 20% difference could be detected with a probability of 80% (the “power” rule).<sup>8</sup> The next generation in bioequivalence metrics was the so-called 75-75 rule. In this metric, the bioavailability ratio for the test product in each individual subject was required to be in the range of 0.75 to 1.25 of the referenced product in 75% of the test subjects.<sup>9</sup> This was the first attempt to assess individual bioequivalence. The test was discarded because of poor statistical properties, but the concept of examining the range of individual bioavailabilities was important.

The bioequivalence metric currently used was put in place in 1992.<sup>10</sup> One form is the two one-sided *t*-test, which examines the hypothesis that the difference between the means (AUC or  $C_{\max}$ ) is either greater than or less than 20% of the mean of the referenced product. This is equivalent to the hypothesis that the 90% confidence interval about the difference between the two means does not exceed  $\pm 20\%$  of the reference mean. A subsequent modification of this approach incorporated the assumption that AUC or  $C_{\max}$  values are usually log-normally distributed rather than normally distributed. Therefore, to maintain an equal interval on either side of the ratio of means of the log-transformed values, the bioequivalence limits of the confidence interval are between  $-20\%$  and  $+25\%$ . These bioequivalence limits are sometimes referred to as the “goal posts.” It has been suggested that the goal posts might be narrower for critical-dose or narrow therapeutic range drugs, and wider for higher variable drugs (that are not narrow therapeutic range drugs).<sup>11</sup> This metric, which focuses on population means, compares the average bioequivalence between the two products. Many individuals mistakenly interpret this metric as requiring that the mean bioavailability (rather than the confidence intervals) of the comparator must be within 80% and 125% of that for the reference product. Operating under such misinterpretation, these individuals purport that as much as a 45% variation in mean bioavailability can be expected for products. Actually, in the first 224 post-1962 drugs approved over the 2-year period after the Waxman-Hatch Act, the observed mean bioavailability differences between the generics and innovator products using this metric varied

by only about 3.5% (the range was -14% to +19%).<sup>12,13</sup>

A new bioequivalence metric has been proposed recently by the FDA. The terms of this metric allow assessment of population and individual bioequivalence rather than average bioequivalence alone.<sup>1</sup> It measures the difference in means of bioequivalence data for reference and test products, the difference in intrasubject variability for reference and test products, and the subject-by-formulation interaction. This metric uses a replicate crossover design in which the patient receives the drug at least twice to determine intrapatient variability for each product and subject-by-formulation interaction.<sup>1</sup>

#### *Issues of Bioequivalence*

In the 1970s, several reports of bioinequivalence were published about drugs such as phenytoin, steroids, and digoxin.<sup>14</sup> However, since the emergence of more stringent bioequivalence testing, the number of these reports has dropped. However, because more immunosuppressive drugs are becoming available, recommendations should be in place.

#### *Concerns of the Participants*

Conference participants were concerned about the exclusion of certain immunosuppressive drugs from lists of critical-dose drugs, the applicability of currently used bioequivalence standards to special populations, and the difficulties that might be encountered with indiscriminate generic substitution. Data were reviewed showing that bioavailability of innovator drugs or generic drugs can differ greatly in subpopulations from bioavailability established in normals.<sup>15,16</sup> Current studies of bioequivalence now performed in normal, healthy volunteers may not highlight these differences.

Conference participants agreed that introducing generic immunosuppressant drugs into the marketplace is beneficial. Such drugs, if safe and effective, have considerable cost-related benefits. Lower-cost alternatives may improve adherence to therapy for patients who cannot afford innovator drugs, provide an incentive for manufacturers of innovator drugs to reduce the price of their products, provide an increased duration of therapy for patients with capped medical benefits, and create an incentive for Congress to

extend Medicare payments for the life of the graft.

Conference participants supported appropriate generic drug substitution except when that substitution could jeopardize patient outcomes. Although current FDA requirements for the establishment of bioequivalence for generics do exist, certain safeguards should be in place to prevent poor outcomes that could result from inappropriate generic immunosuppressant substitution. The following are areas of concern and recommendations to address these issues.

### LIMITATIONS OF CURRENT BIOEQUIVALENCE TESTING

#### *Issues Surrounding Generic Equivalence*

The FDA is aware of concerns about generic substitution and is reviewing its methodology for establishing bioequivalence.<sup>1,17</sup> Although the FDA has concluded that there are no documented cases in which an approved generic product could not be used interchangeably with the corresponding brand-name drug, there may be particular circumstances in which substitution of therapeutically equivalent drugs causes important differences in effect for individual patients.<sup>13,18</sup> Reports of differing clinical outcomes when patients were switched between generics and brand-name products have been published.<sup>15,20-22</sup>

Bioequivalence testing for immunosuppressive drugs, such as cyclosporine, is particularly important because such agents meet many of the criteria for critical-dose drugs (discussed later).<sup>19</sup> Although the FDA does not officially support approaching one therapeutic class of drugs differently from any other class, it has proposed the use of alternative methods for evaluating "narrow therapeutic range drugs."<sup>1</sup> We propose that the FDA recognize critical-dose drugs and believe that the proposed changes in bioequivalence testing will improve the assessment of critical-dose drugs. Moreover, we support the FDA's giving special consideration to testing of narrow therapeutic range drugs.

#### *Recommendations*

1. Critical-dose drugs, as defined by conference participants and the literature, share the following characteristics:
  - Narrow therapeutic range<sup>19,23</sup>

- Requirement for blood level monitoring<sup>19</sup>
  - Dosing based on body weight or other highly individualized dosing requirements<sup>23</sup>
  - Serious clinical consequences of overdosing (toxicity) or underdosing (lack of effect)<sup>19,23</sup>
  - Steep dose-response relationship for either efficacy or toxicity or both<sup>19,23</sup>
2. The immunosuppressive agents cyclosporine and tacrolimus should be included in lists of critical-dose drugs.<sup>24-27</sup> In the future, new immunosuppressive agents should be evaluated to determine whether they also meet these criteria.
  3. For critical-dose drugs, replicate studies to determine intrasubject variability and subject-by-formulation interaction should be required as part of the approval process for both innovator drugs and their generic counterparts.<sup>4</sup> The application of the recently proposed changes in the FDA bioequivalence metric would satisfy these requirements.
  4. Because clinical results are the key end point, research efforts should be directed at finding practical indicators of clinical effects so that the actual therapeutic efficacy of drugs can be more readily compared.

#### *Issues Surrounding the Relevance of Study Populations*

Bioequivalence is tested in healthy, young, usually male volunteers. However, drug behavior in healthy individuals may not accurately predict the behavior in patient subgroups. Differences in the clinical efficacy of innovator drugs are documented among patient subpopulations that vary in metabolism from normal volunteers. For instance, a wide range of factors such as demographics, disease state, food, and drug interactions affect the bioavailability of cyclosporine.<sup>25,28,29</sup> Similarly, studies comparing branded versus generic formulations of levothyroxine, verapamil, and cyclosporine have shown that physiological differences among patients were associated with variable degrees in the bioavailability and clinical effects of these drugs in various subpopulations.<sup>15,30</sup>

The FDA has recognized the difficulty in gen-

eralizing population results to subgroups and has begun to address this issue in its new metric. The FDA recognizes that patients whose absorption or first pass does not match that of healthy volunteers may not just be statistical outliers but may in fact represent a subpopulation for whom the bioavailability of two products is markedly different. For such patients, the products might not be bioequivalent even though these agents can be bioequivalent for most of the population.<sup>1</sup> The FDA has introduced the subject-by-formulation interaction into its new proposed bioequivalence metric to address this issue.

The behavior of drugs in subpopulations with altered absorption (bioavailability) should be studied. Although the FDA is working to establish bioequivalence in outliers who may represent important subpopulations, current regulations of the agency do not require such studies. Yet, clinicians need such information when treating individual patients. Although it would be impossible to test bioequivalence in every potential patient subgroup, we recommend that the FDA individualize the requirements for bioequivalence testing for certain drugs. In many circumstances, the patient characteristics associated with altered bioavailability of a particular drug have already been established, quite often in the innovator literature. Therefore, potential outliers can be anticipated, and including them in bioequivalence testing is important in adequately comparing two products.

#### *Recommendations*

1. For critical-dose drugs, replicate studies to determine subject-by-formulation interactions should be required as part of the approval process for both innovator drugs and their generic equivalents. The application of the recently proposed changes in the FDA bioequivalence metric would satisfy these requirements.
2. The FDA should request that generic manufacturers obtain bioequivalence data in subpopulations of patients for whom, based on evidence in the literature, the drug is likely to exhibit bioavailability that differs substantially from the norm.

### SAFE AND EFFECTIVE USE OF GENERIC IMMUNOSUPPRESSANT DRUGS

The safe and effective use of generic immunosuppressant drugs must be accompanied by a system of checks and balances. Currently, most regulations to ensure that generic substitution is practiced in a responsible manner are made and enforced at the state level.<sup>18,31</sup> Those regulations vary from state to state, which has led to inconsistency in substitution practices and may cause confusion when trying to evaluate them on a broad level.

A major concern is that a prescribing physician might not know when a switch is made to a generic, to a brand name, or to a different generic. In such cases, the physician would not be alerted to the possible clinical consequences of the switch. Another concern is involvement of patients in substitution decisions. Patients view participation in treatment decisions as important to maintaining their autonomy.<sup>32</sup>

Substitution practices should be regulated to ensure consistency in policy. Potential safeguards are listed.

#### *Recommendations*

1. The health care provider should educate the patient about generic drugs and should include the patient in the decision of whether to switch drugs.<sup>14</sup>
2. The pharmacist should inform the prescribing physician and patient whenever a prescribed immunosuppressive drug for a transplant patient is to be switched. No therapeutic drug substitution of a critical-dose drug should be allowed without the approval of the prescribing physician or the patient.<sup>14</sup>
3. Physicians should seek information about the bioequivalence data for the agents they prescribe. When informed physicians are concerned about maintenance of consistent drug regimens or about bioequivalence of generic drugs, they should exercise their option to request that substitution not be made (in whatever manner is necessary to do so in that state) for such prescriptions.
4. Patients should be taught how to identify the prescribed dosage form, and they should be instructed to alert the physician if a drug is substituted.
5. The FDA should require that the appearance of all medications be unique and easily identifiable to help patients distinguish among drug products.
6. Because of the potential consequences arising from differences in bioavailability or intrasubject variability with different products of critical-dose drugs, physicians should consider instituting appropriate monitoring (including blood levels if necessary) whenever patients are switched from one generic formulation to another, from an innovator drug to a generic, or from a generic to an innovator.
7. The health care team should report adverse events with innovator and generic drugs to the FDA and the drug's manufacturer and document this information in the patient's records. The prescriber should also consider informing third-party carriers.

#### CONCLUSION

Conference participants were concerned about the exclusion of certain immunosuppressive drugs from lists of critical-dose drugs, the applicability of currently used bioequivalence standards for special populations, and the difficulties encountered with substitution. Of particular concern was that the pharmacokinetic profiles of critical-dose generic drugs among subpopulations of transplant patients may differ substantially from those found in normal, healthy volunteers. These differences may lead to unanticipated differences in clinical response when generic drugs are substituted for innovator drugs in these subpopulations.

Because safe and effective generic immunosuppressive drugs have many potential cost-related benefits, the conference participants welcomed their introduction in the field of transplantation. However, certain safeguards must be adopted to prevent poor outcomes from inappropriate generic substitution of these drugs. Of first priority is scrutiny of the approval process. It is further recommended that the FDA hold narrow therapeutic range drugs to more stringent standards of bioequivalence assessment than those used for other therapeutic classes, requiring that the drug manufacturer conduct replicate studies of intrasubject variability and subject-by-formulation interactions in addition to conventional bioavailabil-

ity studies. Furthermore, the generic manufacturer should be required to show bioequivalence in target populations in which the innovator drug has shown substantial pharmacokinetic variation. Once approval has been granted for a given drug, consistent substitution practices should be adopted by all involved parties as part of their shared responsibility for the safe and effective use of these drugs in the care of transplant patients.

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