# Bioequivalence testing of immunosuppressants: concepts and misconceptions

Uwe Christians[1], Jelena Klawitter[1] and Claudia F. Clavijo[1]

[1]*Clinical Research and Development, Department of Anesthesiology, University of Colorado Denver, Aurora, Colorado, USA*

**Immunosuppressants are considered critical dose/narrow therapeutic index drugs and there is the lingering suspicion among physicians and patients that generic versions may differ in quality and therapeutic efficacy from the brand name drug. The innovator's and the generic active drug molecule are exactly the same and are produced following exactly the same tight rules of good manufacturing practice. Upon oral administration, the drug molecule separates from the formulation and passes the membranes of gut mucosa cells; from this point on, the formulation has no influence on the kinetics of a drug and its biological effects. As formulations may differ, bioequivalence testing in healthy volunteer studies establishes equal relative oral bioavailability. Due to the number of patients required to achieve sufficient statistical power, to test the therapeutic equivalence of two formulations of the same drug with the same bioavailability is an unrealistic goal. An often overlooked fact is that the approval by drug regulatory agencies of several post-approval versions of the innovators' immunosuppressants is based on the identical guidelines used for approval of generics. The FDA has issued specific guidelines describing the requirements for approval of generic versions of tacrolimus, sirolimus, and mycophenolic acid. The standard average bioequivalence approach is recommended and in the cases of tacrolimus and sirolimus, the effect of food should also be tested. No studies in the patient population are requested. Immunosuppressants are not regarded as drugs that require a special status to establish bioequivalence between generic and the innovator's versions.**

*Kidney International* (2010) **77** (Suppl 115), S1–S7; doi:10.1038/ki.2009.504

KEYWORDS: bioequivalence; generics; immunosuppressants; narrow therapeutic index; switchability

**Correspondence:** *Uwe Christians, Clinical Research and Development, Department of Anesthesiology, University of Colorado Denver, Bioscience East, Suite 100, 1999 North Fitzsimons Parkway, Aurora, Colorado 80045-7503, USA. E-mail: uwe.christians@ucdenver.edu*

In the United States and many other countries in the world, companies are free to manufacture interchangeable generic products once the innovator's patent protection of a 'brand name' drug expires. However, since the availability of generic versions of brand name drugs, there has always been the lingering suspicion among physicians and patients that generic drugs may differ in quality and therapeutic efficacy and may put patients at risk.[1,2] It cannot be denied that in several cases, such fears have been encouraged by innovators to protect their market share and pricing. Early scientific evidence, mostly from the 1970s, recognized that even when two drug products contained the same active component at the same dose, small changes in the product formulation could result in significant differences in oral bioavailability. Several cases of lack of effect or intoxication after administration of pharmaceutically equivalent generic drug products were reported.[3] As a response to these reports, in 1974, in the United States, the Office of Technology Assessment established the Drug Bioequivalence Study Panel to develop clinical and statistical procedures for establishing bioequivalence between pharmaceutical equivalents. The recommendations were implemented by the Food and Drug Administration (FDA) and codified in 21 CFR Part 320.[4] Pharmaceutical equivalents contain the same active ingredient, are administered by the same route in the same dosage form, and are of identical strength and concentration.[5]

In 1984, the Drug Price Competition and Term Restoration Act[6] permitted the FDA to use a simplified approval process for generic products of drugs, so-called abbreviated new drug applications (ANDA).[7] In summary, a generic drug product has to meet compendial, bioequivalence, and good manufacturing standards.

Although the approval of generics is a tightly regulated and proven process with an excellent safety track record,[5] as of today, frequent arguments against generic drugs mentioned by physicians and patients alike are the following:

- The quality of generics is sometimes lower than that of the originator drug.
- The FDA acceptance limits for generics are 80–125%. This is a potential difference of as much as 45%!
- Generic drugs are tested only in healthy volunteers and may act differently in the target disease population, resulting in uncontrolled clinical risks.

- Generics of so-called 'critical dose' drugs are especially dangerous.

It is the goal of our review to address these arguments in detail.

## BASIC CONSIDERATIONS OF BIOEQUIVALENCE TESTING

Today, demonstration of average bioequivalence between the brand name drug (reference) and a generic drug product (test drug) is a requirement for approval by drug regulatory authorities in the United States[8] and most other countries.

The components of a drug product can be divided into two major components: the drug molecule (this may be the active drug or a prodrug, such as mycophenolate mofetil, which is converted into the active principle in the body) and the drug formulation. Whereas the drug molecule is responsible for therapeutic effects and potential drug-related adverse effects, the only purpose of the formulation is to deliver the drug into the system. It is critical to understand that, on oral administration, the drug molecule is separated from the formulation and passes the membranes of the gut mucosa cells, and hereafter, the formulation has no influence on the kinetics of a drug and its biological effects.

The overall therapeutic/toxicological effects of a drug are determined by two basic principles: its kinetics (pharmacokinetics/toxicokinetics) and its dynamics (pharmacodynamics/toxicodynamics). Pharmacokinetics/toxicokinetics describes the way the body handles the drug molecule, including its absorption, the time-dependent concentration changes of the drug in blood and tissues, and the elimination of the drug from the body. Pharmacodynamics and toxicodynamics describe the effects that a drug has in the body that can treat a disease and/or that may cause toxic effects. This includes the drug molecule's interactions with its target molecules such as enzymes and receptors.

The term bioequivalence describes both equivalence of pharmacokinetics/toxicokinetics and equivalence of pharmacodynamics/toxicodynamics. Bioequivalence is defined as 'the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.'[8] If bioequivalence has been established, drugs will be therapeutically equivalent and will exhibit equivalent tolerability and safety profiles.

The FDA guidance assumes bioequivalence when the same bioavailability can be demonstrated.[8] Oral bioavailability is defined as 'the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action…'. This assumption is correct for the following reason: Once absorbed, a drug molecule's behavior is completely independent of the formulation by which it was delivered across the gut mucosa. This includes its pharmacodynamics (its therapeutic potency and efficacy), its tolerability, safety, and its elimination (clearance) from the body. As the efficacy and safety of an innovator's drug has already been established, the FDA regulations are promulgated without repetition of the same studies of the generic version of the drug, as it contains exactly the same molecular entity as the innovator's product. Oral delivery of a drug may be affected by its formulation, but also by interactions in the gut including the presence of food or gut bacteria, gut motility, and gut disease processes such as infections and inflammation. The only drug-specific component with the potential to differ between an innovator's version of the drug and a generic version is the formulation. The goal of bioequivalence testing is to demonstrate that this is not the case.[9]

As aforementioned, bioequivalence studies typically aim to demonstrate that two pharmaceutical equivalents have similar pharmacokinetics.[10] The standard bioequivalence trial is conducted according to a randomized 2-period crossover design and typically includes between 12 and 36 healthy adults with an appropriate washout between study periods. The key issue in bioequivalence testing is to demonstrate similar oral bioavailability. As pharmaceutical equivalents are orally administered, absolute bioavailability cannot be determined directly. Area under the time concentration curve (AUC) measurements serve as a surrogate for the extent of absorption or systemic exposure. The maximum plasma concentration ($C_{max}$) and the time of its occurrence ($t_{max}$) together characterize the rate of absorption.[11] Test and reference product are considered equivalent when the 90% confidence interval for the true formulation means ($\mu_{test}/\mu_{reference}$) falls within the acceptance limits of 0.8–1.25.[12,13] In practice, the confidence interval approach is carried out using log-transformed data.[14] The 0.8–1.25 bioequivalence acceptance range translates into a difference of $-20$ to $+25\%$ in the rate and extent of absorption between the two drug products. These acceptance limits are arbitrary and are based on the observation that a $-20$ to $+25\%$ difference in the concentration of the active ingredient in blood will not be clinically significant.[5,15] It is important to recognize that it is the upper and lower limit of the 90% confidence interval for the true mean ratios and not only the mean ratio (point estimate) that must be within the bioequivalence acceptance limits.[5] The 90% confidence interval is a measure of total variability, which is influenced by both inter- and intra-individual variability.[16,17] Variability is a factor that has a significant impact on acceptance or rejection in average bioequivalence testing. The width of the 90% confidence interval is dependent on both the magnitude of the within-subject variability of the reference drug and the number of subjects. Bioequivalence testing compares the quality of reference and test formulations. Therefore, the tighter the intra-subject variability of the oral bioavailability of the brand name drug, the more difficult it is for the generic version to meet bioequivalence acceptance criteria.

## IS THE QUALITY OF A GENERIC DRUG THE SAME AS THAT OF THE BRAND NAME DRUG?

The FDA's approval process of generic drugs evaluates chemistry, manufacturing and controls, *in vivo* bioequivalence, labeling,

*in vitro* dissolution, if applicable, and includes inspection and auditing of all facilities. Identical to the innovator's regulatory submission, the manufacturer of a generic drug must submit a chemistry, manufacturing, and control package to the FDA for review. The required testing includes, but is not limited to, quality and purity of the drug, stability of the drug substance and formulated drug, batch reproducibility, and the establishment of a quality system for batch release. Manufacturing of a generic drug, just as for manufacturing the brand name drug, has to comply with the rules of good manufacturing practice.[18]

### Can the difference between the $C_{max}$ and exposure of a brand name drug and a generic really be as much as 45% (between 80 and 125% of the innovator)?

As aforementioned, it is the upper and lower limit of the 90% confidence interval for the true mean ratios and not only the mean ratio (point estimate) that must be within the bioequivalence acceptance limits.[5] To fit the 90% confidence interval within the 80–125% acceptance limits, the generic drug and the innovator have to be almost identical. The only theoretical exception is if the generic drug formulation has a markedly lower variability than the innovator's formulation. However, even then, a deviation of 15% is almost impossible and additional studies would most likely be requested. Indeed, an analysis of 224 approved generic drugs showed the mean difference of the point estimates of the area under the time concentration curves to be within 3.5% of that of the innovator's formulation and 80% of the area under the time concentration curve point estimates to be within $\pm 5\%$ of those of the innovator's formulations.[19] When assessing these numbers, it should also be considered that the bioanalytical assays used for these studies are allowed to have a total imprecision of up to 15% and a between-day accuracy of between 85 and 115%.[20] Even if modern bioanalytical assays usually perform better and samples are run in as few batches as possible to reduce variability, considering that bioanalytical assays still add to the overall variability of the results, it seems reasonable to assume that relative bioavailability of most innovators' formulations and generic formulations is almost identical. Even if the innovator's batches or even the same batch of an innovator's drug is compared, the results are not always exactly the same.[21]

## IS TESTING OF BIOEQUIVALENCE IN THE TARGET DISEASE POPULATION OF ADVANTAGE?

An adjunct question on this topic is why use relative bioavailability as a surrogate marker instead of establishing therapeutic equivalence? It is important to note that it is necessary to establish relative bioavailability in a healthy volunteer population first. To avoid exposing patients to undue risks due to a potential lack of therapeutic efficacy or toxicity, bioequivalence between the innovator drug and a generic must be shown before the drugs can be compared in a patient population. To test for therapeutic equivalence, patients should be randomly divided into two separate study groups, with one group of patients treated with the reference formulation and the other receiving the test product. Parameters included in the analysis would be the incidence and severity of side effects and therapeutic efficacy. An acceptable sensitivity would be about $\leqslant 10\%$ difference between the study groups receiving the test and reference formulation. Taking that into consideration, after a successful comparison in healthy volunteers, two bioequivalent drug formulations will be compared. The number of study subjects required to result in reasonable statistical power ($\geqslant 80\%$) would easily exceed those required for phase III clinical trials and be prohibitive in terms of time and costs.[22] Although several therapeutic efficacy studies between alternative bioequivalent formulations of immunosuppressants have been described, it is reasonable to assume that, statistically speaking, these studies were severely underpowered and would not have detected potential differences. A good example of such a study was the comparison of the efficacy and safety of Neoral with that of Sandimmune in 466 renal transplant patients.[23] Although Sandimmune and Neoral are not bioequivalent, the overall incidence of adverse events was similar, even with an increase in the exposure of patients to cyclosporine in the test group after a 1:1 switch to Neoral. In addition, there was no difference in kidney function. Nephrotoxicity is a frequent side effect of cyclosporine. The results of this study comparing two not-bioequivalent cyclosporine formulations indicated that the detection or exclusion of differences in the safety and efficacy of two bioequivalent cyclosporine formulations with reasonable sensitivity and statistical power would be practically impossible using this quantity of patients.

The few studies that claimed to show a difference[24–26] were statistically underpowered and/or flawed in other ways and have not prompted drug regulatory authorities to take any action.

With very few exceptions such as direct interactions of the formulation with drugs in the gut lumen with drugs such as chelators, resins, or ion exchangers, once the drug is absorbed, most clinically significant drug–drug interactions occur in the gut and/or the liver, at the drug-metabolizing enzymes, and/or active drug transporters. Again, on absorption, the drug molecule will behave in exactly the same manner after delivery, regardless of its formulation. For this reason, the effects of genetic polymorphisms, drug–drug and disease–drug interactions in the liver or other organs will be similar and independent of whether the active molecule was delivered by a generic or the innovator's formulation. It should be noted that ethnic differences in pharmacokinetics are mostly due to different distribution patterns of polymorphisms of drug-metabolizing enzymes and/or active drug transporters in specific populations.

A single isolated report showed that sirolimus absorption was affected differently by generic than by the innovator's cyclosporine formulations.[27] Intestinal drug–drug interactions are a general problem in transplantation and can occur when foods, herbal drugs, and other drug formulations are taken in at the same time as the immunosuppressants. Changing the cyclosporine concentration will also affect

sirolimus blood concentrations. This will happen with both the innovator and generic formulations. Even the most extensive new drug development will not be able to predict or study all possible interactions. Most of the coadministered drugs with the potential to interact with immunosuppressants have never been specifically tested in a transplant population but, regardless, they have safely been used. Drug–drug interactions greatly depend on factors such as pharmacogenomics, the presence of other drugs, and liver function. The extent of a drug–drug interaction will depend on the nature, dose, and duration of administration of the interacting drug rather than on the formulation of the immunosuppressant, and will also require blood concentration measurement and possibly dose adjustments. Owing to confounding factors, it is more difficult to detect potential differences between two formulations in a patient population that exhibits significant variability. For this reason, a rigorously controlled study in healthy individuals is more likely to show potential differences between a brand name immunosuppressant and a generic version than studies in the more variable and less well-controlled target patient population.

## DOES BIOEQUIVALENCE TESTING OF NARROW THERAPEUTIC INDEX DRUGS REQUIRE TIGHTER RULES?

The terms 'narrow therapeutic' and 'critical dose' drugs are often used interchangeably. Benet and Goyan[28] defined narrow therapeutic index drugs as 'those for which small changes in pharmacokinetic response lead to marked changes in pharmacodynamic response.' This means that, in general, narrow therapeutic index drugs have a steep dose–response curve (for a detailed discussion, see Reference 29). The FDA defines narrow therapeutic index drugs as follows: (1) there is a less than twofold difference in median lethal dose ($LD_{50}$) and median effective dose ($ED_{50}$) values or (2) there is less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in blood, and (3) safe and effective use of the drug product requires careful titration.[29,30] There seems to be a general consensus that immunosuppressive drugs such as cyclosporine, tacrolimus, the proliferation signal inhibitors such as sirolimus and everolimus, and probably also mycophenolate and its derivatives should be considered narrow therapeutic index drugs.[31] On the other hand, highly variable drugs have been defined as a drug with a within-subject variability equal to or exceeding 30% of the maximum concentration ($C_{max}$) or the area under the time concentration curve.[16] Approved high variability drugs are generally safe and often have relatively flat dose–response curves. In the case of drugs with high within-subject variability and a steep dose–response curve, patients will frequently experience episodes of a lack of therapeutic effect (drug exposure too low) or toxicity (drug exposure too high). These drugs typically fail during clinical drug development.[28] Therefore, approved drugs with a steep dose–response curve such as narrow index drugs have relatively low within-subject variability. Although bioequivalence testing for highly variable drugs is a challenge that requires large numbers of subjects to achieve adequate statistical power, testing the bioequivalence of narrow therapeutic index drugs is comparatively straight forward. It is important to remember that the within-subject variability of the reference drug determines the bioequivalence acceptance limits. Low intra-subject variability of the reference drug raises the bar for the test formulation and the generic version must meet these tight acceptance criteria. Although the significant subject–formulation interaction of highly variable drugs may cause a subset of subjects to respond differently to the test and reference formulations, this is hardly ever the case with two bioequivalent formulations of a narrow therapeutic index drug. In addition, owing to the narrow inter-subject variability, testing would reveal that the formulations are not bioequivalent. However, the validity of average bioequivalence and the 0.8–1.25 acceptance range for narrow therapeutic index drugs has been questioned repeatedly. Although tighter acceptance criteria such as an acceptance range of 0.9–1.12 or 0.9–1.11 have been proposed and are required by some drug agencies such as Health Canada[32] and the European Medicines Agency,[33] respectively, narrow therapeutic index drugs typically have no problems meeting these more stringent criteria.[28] In the United States, it is believed that the stringency of present requirements for bioequivalence excludes the possibility of therapeutic problems resulting from drugs with dosage forms that meet regulatory criteria, including those with a narrow therapeutic index.[5,28,30] This is also reflected by recently published FDA guidances for bioequivalence testing of tacrolimus, sirolimus, and mycophenolic acid formulations. These guidances do not contain any special requirements other than for testing for food effects in the cases of tacrolimus and sirolimus.[34–36]

Several publications state that cyclosporine is a drug with a high inter- and intra-individual variability.[21] The high inter-individual variability of cyclosporine bioavailability and pharmacokinetics is well documented and, in part, is due to polymorphisms of cytochrome P4503A enzymes and p-glycoprotein (ABCB1) haplotypes (for more details see).[21,37–39] There is no evidence in literature that cyclosporine in the innovator's Neoral formulation itself has a high within-subject (intra-individual) variability. This finding is consistent with most narrow therapeutic index drugs and different from the now obsolete Sandimmune formulation. In fact, the within-subject variability reported in literature is less than 20% and in several publications even less than 10%.[21] Within-subject variability in transplant patients is usually caused by drug–drug, drug-disease, and food–drug interactions. This accounts for therapeutic drug monitoring and blood concentration-guided dose adjustments. The situation for the other immunosuppressants is similar.

## NEW DRUG FORMULATIONS AND BIOEQUIVALENCE TESTING – THE SAME RULES APPLY FOR INNOVATORS AND GENERIC MANUFACTURERS

Switchability signifies that once bioequivalence is established, patients can be freely switched from one version of an immunosuppressant to another without experiencing clinically relevant loss of efficacy or exposure to an increased risk

**Table 1 | Bioequivalence of modifications and new development of formulations of immunosuppressants by innovator companies**

| Formulation change | Bioequivalence[References] |
|---|---|
| *Cyclosporine* | |
| Sandimmune oral solution → soft gelatin capsule | Most likely not[42–45] |
| Sandimmune oral solution → neoral oral solution | No[23,46–49] |
| Neoral oral solution → capsule | Yes[50] |
| *Sirolimus* | |
| Capsule → tablet | Failed pharmacokinetic bioequivalence, therapeutic equivalence was established[51] |
| *Everolimus* | |
| Adult → pediatric formulation | No[52] |
| *Tacrolimus* | |
| 5 mg → 1 mg capsule | First failed average bioequivalence, then met individual bioequivalence criteria[53,54] |
| Prograf → extended release formulation | Formulations intended to be different, therapeutic equivalence shown[55–60] |
| *Mycophenolate mofetil* | |
| Mycophenolate Mofetil (Roche, Basel, Switzerland) → enteric coated mycophenolic acid (Novartis, Basel, Switzerland) | Formulations intended to be different, therapeutic equivalence shown[61–64] |

of toxicity.[40] The question of switchability arises not only with generic substitution, but also occurs with postapproval changes in the formulation and manufacturing of an approved drug product by an innovator or a generic manufacturer.[41] Several examples are listed in Table 1. Although not every one of these changes has resulted in bioequivalent formulations, and some of these formulation changes were never intended to be bioequivalent, transplant patients have been switched between these formulations without a reported increase in clinical complications. Although the sirolimus tablet formulation failed to meet pharmacokinetic bioequivalence criteria when compared with the oral solution, therapeutic equivalence was demonstrated in a larger multicenter trial.[51] A seemingly minor change to the tacrolimus formulation (five 1 mg capsules versus one 5 mg capsule) failed average bioequivalence testing but passed individual bioequivalence testing,[53,54] an alternative bioequivalence strategy that was accepted and tested by the FDA at this time.[41] This new formulation was ultimately marketed and it is safe to assume that many patients have substituted 1 mg with 5 mg capsules and *vice versa* without any hesitations and problems.

It is reasonable to expect that switching between two bioequivalent formulations manufactured by the innovator will have the same risks, or a better lack hereof, as switching between a brand name drug and a bioequivalent generic.

## CONCLUSIONS

The extent to which the FDA and most foreign drug agencies' standard bioequivalence criteria can be applied to cyclosporine formulations and other immunosuppressants considered a narrow therapeutic index or critical dose drugs is a topic addressed by several authors, and discussed at several consensus conferences and in opinion and review papers.[21,31,65–72] The number of publications alone implies the multitude of opinions and lack of consensus. These 'guidelines' and recommendations differ significantly and can often bear great contradictions between each other. A disturbing aspect of some of these recommendations is that they are based on unproven principles and on no solid set of data. On the other hand, recommendations and guidances issued by regulatory agencies are often based on extensive safety registries and databases.

To summarize the discussion above, the generic drugs approved by the FDA and other regulatory agencies

- contain the identical active molecule as the innovator's version of the drug;
- are manufactured following precisely the same quality standards;
- have to meet bioequivalence criteria that can only be met if both the point estimate and the 90% confidence interval of the true mean ratios fall within 80–125% acceptance limits;
- can be tested adequately in healthy volunteers, whereas testing in the target patient population will not necessarily generate additional information or uncover previously unknown risks.

In addition, the current average bioequivalence acceptance limits and testing strategies have proven to be sufficient and safe for the approval of narrow therapeutic drugs. This is reflected in recent guidances for the bioequivalence testing of tacrolimus, sirolimus, and mycophenolic acid released by the FDA on the basis of establishing bioequivalence and discluding any special requirements.

Because of the lower costs of development and competition in the market, the price of generic drugs is usually significantly less than that of the innovator's product before the availability of generics. It is generally agreed that prescribing and utilizing generic drugs reduce the cost of drug therapy. Lower-cost alternatives may improve adherence to therapies for patients who cannot afford innovator drugs and provide an increased duration of therapy for patients with capped medical benefits. In this manner, approved generic drugs have the potential to improve quality of care.

## DISCLOSURE

UC has received lecture fees from TEVA and is lobbying against generics carve-out bills in several US states (Barr Laboratories, Montvale, NJ, USA). The remaining authors declare no conflict of interest.

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