Bioequivalence testing of immunosuppressants: concepts and misconceptions

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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.

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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,