ELSEVIER

Understanding Bioequivalence Testing

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APPROVAL of generic drug products in the United States is based on manufacturer's submitted data demonstrating that the generic product is bioequivalent to the pioneer (innovator) drug product. Every prescription written for a generic drug requires an act of faith by the prescriber that any one of the several available products will be therapeutically equivalent to the innovator (brand name) product. Concerns about this act of faith have been expressed for many years, but usually by individuals with a poor understanding of the requirements for generic formulations and the studies undertaken to receive marketing approval in the United States. Although this presentation will focus on US regulatory processes, the basic principles are applicable to the generic approval process throughout the world.

Bioequivalency testing involves comparison of measures of bioavailability of the generic and innovator formulations. Bioavailability is characterized by "the rate and extent to which the active drug ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action."[1]

Bioequivalent drug products must be pharmaceutically equivalent and display comparable bioavailability when studied under similar experimental conditions. Pharmaceutical equivalents contain the same active ingredient, are administered in the same dosage form by the same route of administration, and are of identical strength or concentration. For pharmaceutical equivalents to be bioequivalent, "the rate and extent of absorption of the test drug must not show a significant difference between the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredients under similar experimental conditions as either a single dose or multiple doses."[2]

Of greatest concern to the clinician is the definition of therapeutic equivalence. The Food and Drug Administration (FDA) provides the following definition: "drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[2] It is doubtful that anyone would disagree with this definition. However, the point of contention relates to what studies are necessary to have confidence that a generic drug product will "be expected to have the same clinical effect and safety profile" as the innovator product. In the United States, the expectation of the same clinical effect and safety profile of the two drug products is based on a standard bioequivalence study that is conducted in a crossover fashion in a small number of volunteers, usually comprising 24 to 36 healthy normal adults. Single doses of the test and reference drugs are administered and blood or plasma levels of the drug are measured over time. Measures of area under the concentration-time curve (AUC) and the peak blood or plasma concentration (C_{max}) are examined by statistical procedures. Bioequivalence of two formulations of the same drug substance requires equivalence with respect to the rate (tested by comparing C_{max}) and the extent (tested by comparing AUC) of drug absorption. The FDA regulations state that "two formulations whose rate and extent of absorption differ by −20%/+25% or less are generally considered bioequivalent. The use of the −20%/+25% rule is based on a medical decision that, for most drugs, a −20%/+25% difference in concentration of the active ingredient in blood will not be clinically significant."[2] The basis for the above statement and the history of the present regulation are reviewed by Sheiner[3] and Benet and Goyan.[4] Unfortunately, the above statement concerning the limits of −20%/+25% is out of date and misleading for clinicians. The statement appears to imply that on average a generic formulation can be 20% less bioavailable than the innovator product or 25% more bioavailable. Furthermore, it is easy to extrapolate from this statement to a concern that a patient could potentially be switched from one generic product that is 20% less available than the innovator product to a second generic product that is 25% more available than the innovator, a potential 45% change in drug delivered between two approved generic formulations. Such arguments are often heard as a rationale from those who oppose switching patients from innovator formulations to less costly generic products. However, in actual fact, the statistical criteria for approval of a generic formulation are not based upon differences in average values for extent (AUC) and rate (C_{max}). The

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Table 1. An Example of the Test Vs Reference Results of a Highly Variable Drug

	AUC	C_{max}
Number of subjects	36	36
Test	224 ± 146	80 ± 62
Reference	212 ± 129	79 ± 48
Ratio of means (test/reference)	1.05	1.01
90% Confidence interval*		
Lower limit	0.72	0.87
Upper limit	1.07	1.21

Note: A highly variable drug is defined as having a coefficient of variation >30%. Here CVs are >60%.
*The 0.80–1.25 criteria is applied to the 90% confidence interval, not the ratio of means.

Table 2. Bioequivalence Studies for New Molecular Entities Approved by the FDA From January 1, 1981 through December 31, 1990

Total approved	220
For oral administration	97
Bioavailability requirements waived (no or minimal absorption)	3 (3.3%)*
Unavailable or insufficient data to judge	7
Final marketed formulation same as clinical trial	34 (37.8%)
Final marketed formulation different from that in clinical trial (for 50 new molecular entities bioequivalence tested in vivo)	53 (58.9%)

*Percentage falling into each category where sufficient data are available. (Data from Benet and Goyan.[4])

−20%/+25% rule is only satisfied by statistical criteria which show that the 90% confidence interval around the ratio of measured parameters will fall within the accepted 0.8 to 1.25 range. That is, in practice, two one-sided statistical tests are carried out using log-transformed data from the bioequivalence study to show that the 90% confidence interval for the ratio of the generic to the innovator for AUC and the ratio for C_{max} are within the limits of 0.8 and 1.25 (ie, −20%/+25%). This requirement that the 90% confidence interval for the generic product relative to the innovator fall within −20%/+25% is very different than the implied criteria that the ratio of the average values fall within this interval.

For a highly variable drug (coefficients of variation greater than 30%), even when the ratio of means (test/reference) is very close to 1.0, the product can still fail the FDA bioequivalence requirements (Table 1). In the example shown in Table 1, the ratio of means for AUC was 1.05 and the ratio of means for C_{max} was 1.01. However, the test product is not bioequivalent to the reference product since the lower limit of the 90% confidence interval for AUC (ie, 0.72) is outside of the 0.8 to 1.25 acceptable range. Note that even for C_{max} where the ratio is 1.01, the upper limit of the 90% confidence interval for C_{max} (ie, 1.21) approaches the maximum acceptable 1.25 value. Thus, clinicians should have a much greater confidence in the equivalence of approved generic products when they realize that the statistical criteria are based on the 90% confidence interval, not the means for AUC and C_{max}.

In 1987, after only 2 years of experience with the new law for approval of generic drugs, Nightingale and Morrison[5] reviewed the data for 224 generic drug products approved up to that time. They noted that the mean difference in AUC between approved generic products vs the innovator product was 3.5% and that the percentage of products within ±5% of innovator AUC was about 80%. Only 1 of 224 approved products had an AUC greater than 15% different from the innovator. It should be noted that the products reviewed by Nightingale and Morrison were accepted on the basis of a different statistical criteria than the 90% confidence interval now required. Most likely the product with a 15% difference in AUC would not pass the present more restrictive statistical requirements. It has been reported that the FDA is currently reanalyzing over 2000 generic drug products that have been approved since the 1987 evaluation. Although the results are not final, the early calculations suggest that differences between approved generic products and innovator products will be minimal, certainly on average less than 5%.

One of the major issues often raised by those opposing a particular generic product is that the studies required for bioequivalence do not include clinical tests within the intended patient population. Many clinicians and patients wrongly presume that new drug products coming to the market have been evaluated in patient populations. Benet and Goyan[4] have pointed out that the community of concerned health professionals is apparently unaware that the majority of new oral drug products on the market have been approved based on a bioequivalence study in healthy volunteers. That is, the dosage form that is finally approved by the regulatory agencies is usually not the one used in clinical efficacy studies. In such cases, the innovator is required only to prove to the regulatory agencies that the final marketed form is bioequivalent to that formulation used in the efficacy studies. In November 1990, in testimony before the Edward's Committee recommending changes in the FDA,[6] Benet pointed out that approval of the majority of new orally administered drug products was based on the same bioequivalency criteria that are used for the approval of generic drugs. At his request, the FDA reviewed the new molecular entities approved during the decade of the 1980s with the results presented in Table 2. As suspected, only 38% of those products approved for oral administration used the original market formulation in the pivotal clinical trials. In contrast, 59% used different experimental formulations, and therefore were required to prove bioequivalence of the formulation to be marketed with that used in the trials. Thus, for the majority of new drugs administered orally during the past decade, clinical studies were not carried out on the marketed formulation, just as is the case with generic drugs.

Recently, there has been increased interest in bioequiva-

lency issues with the contention being raised that the present requirements are not adequate for narrow therapeutic index (NTI) drugs. Officials at the FDA have vigorously denied that the present regulations are not appropriate. However, clinicians may hear a great deal of discussion concerning "population" vs "individual" bioequivalence. These terms are translated into issues related to "prescribability" and "switchability." It has been proposed that the present bioequivalence criteria based on a single dose crossover of the test and reference products will assure only that a particular generic product will be equivalent to the innovator for the population as a whole, that is, it is "prescribable." In contrast, of greater importance is the assurance of bioequivalence in a patient already stabilized on the innovator product when the patient is switched from the innovator drug product to the generic. Theoretical proposals requiring replicate design studies, ie, studies where each subject in a bioequivalence study receives the generic formulation twice and the innovator formulation twice, thereby providing measures of intrasubject variability, are needed to assure switchability. In my opinion, individual bioequivalence is a promising, clinically relevant method which should theoretically provide further confidence to clinicians and patients that generic drug products are, indeed, equivalent in an individual patient. However, as of this time, little prospective data exist to validate this theoretical approach and to provide confidence to the scientific and clinical community that the methodology required and the expense entailed would be justified. Currently, individual bioequivalence is a theoretical solution to solve a theoretical clinical problem. There is no evidence of a clinical problem, either a safety or an efficacy issue. Furthermore, there is no evidence that individual bioequivalence would solve the problem if it did exist. What is needed is the generation of a large database which would provide the FDA and drug company scientists with the necessary information to make a reasoned consensus judgement as to the appropriate criteria for individual bioequivalence.

In conclusion, this report has provided background information on how bioequivalence studies are carried out at present, the limits of differences allowed for acceptable products, and some history concerning actual differences between generic and innovator products as provided by the FDA. Additionally, it has been shown that innovator manufacturers often use the same test required for approval of a generic product to receive market approval for the innovator product. Finally, the controversial issues relating to individual bioequivalence were reviewed, particularly with reference to NTI drugs, and as have been raised with respect to generic cyclosporine. The following presentations in this symposium address specific issues related to immunosuppressive drugs.

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