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Commentary

Determination of *in Vivo* Bioequivalence

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The May and June 2001 issues of *Pharmaceutical Research* contained three articles related to the determination of *in vivo* Bioequivalence (1–3). The articles discussed: (a) the bioequivalence of highly variable drugs, (b) novel metrics for direct comparison of bioequivalence study plasma curves, and (c) the role of a microemulsion vehicle on cutaneous bioequivalence.
An analysis of the relationship and potential impact of these articles on their respective areas of bioequivalence will be addressed in this commentory.

KEY WORDS: bioequivalence; highly-variable; metrics; cutaneous pharmacokinetics.

EVALUATION OF THE BIOEQUIVALENCE OF HIGHLY-VARIABLE DRUGS AND DRUG PRODUCTS

The analysis of drugs with high intra occasion variability has proved to be a problematic area in bioequivalence. Analysis of studies exhibiting subject-by-formulation interactions was one of the main rationales for the development of individual bioequivalence (IBE). The authors in the current paper are using the concept of scaling to the reference product, which has been proposed for IBE, and proposing that it can be applied to the calculation of average bioequivalence.

The article examines two current and one proposed new method for calculating the 90% confidence intervals for drugs that are considered to be highly variable (i.e., with an intra-subject percent coefficient of variation above 30%). The methods discussed were: (a) unscaled average bioequivalence, (b) reference-scaled individual bioeqiuivalence and (c) residual variance (σ^2_{SC}) or reference variance(σ^2_{WR})-scaled average bioequivalence. A recent *Guidance for Industry-Statistical Approaches to Establishing Bioequivalence* published by the FDA (4) recommends unscaled average bioequivalence and reference-scaled individual bioeqiuivalence as acceptable methods for calculating the 90% confidence intervals for bioequivalence studies. Scaling allows the bioequivalence acceptability limits to be linked to the observed reference variance. The new concept proposed by these authors is the application of scaling to average bioequivalence utilizing either the residual variance for a two-way crossover study or within subject variance for a four-way crossover study. The end result of the proposal would be to multiply the average BE limit (θ_A) by either σ^2_{SC} or σ^2_{WR} with the new limit equal to $\theta_A \times \sigma^2_{SC}$ or $\theta_A \times \sigma^2_{WR}$, respectively. This effectively expands the bioequivalence limit. The advantages claimed for this approach to the evaluation of highly variable drug products are (1) increased statistical power, and (2) insensitivity to both test and reference variance and subject-by-formulation interactions.

However, in my view, more data need to be collected before the method can be considered for adoption as a requlatory standard, to establish an appropriate preset limit (θ) for scaled average bioequivalence and its type II error level (i.e., consumer risk). Also its performance vs. that of the reference-scaled individual bioeqiuivalence method needs to be studied further. Once this information is obtained, the proposed method can then be properly evaluated for its true merit and application to the bioequivalence determination of highly variable drug products.

NOVEL DIRECT CURVE COMPARISON METRICS FOR BIOEQUIVALENCE

Cmax has been used to indicate rate of absorption and more recently peak exposure in bioequivalence studies. It is a belief by many scientists in the area of bioequivalence that a better measure for rate is needed. Consequently, there have been proposed metrics such as Cmax/AUC to define "rate of absorption" in bioequivalence studies. Despite the many discussions in the literature the new metric was never adopted. The current authors have developed novel direct curve comparison methods using plasma concentrations speculating that once validated these procedures may have advantages over the current metrics for determining rate of absorption.

There are two traditional metrics used to assess bioequivalence- AUC and Cmax which are used to measure "extent" and to indicate "rate" of absorption, respectively. A recent approach emphasizes the shape of separate parts of the plasma drug concentration vs. time curve by introducing the concepts of early, total and peak exposure (5). The metrics proposed to measure these exposures are partial area under the curve, area under the curve to the last quantifiable concentration, and Cmax, respectively. This paper has introduced four new direct curve comparison methods (Rho, Rho_m, $Delta_n$ and $Delta_s$) which utilize all of the plasma profile data after it is weighted by the sum of the test and reference con-

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centrations. These methods either compare the test and reference concentrations directly, or compare the ratios of the test-to-reference concentrations. AUC and Cmax, despite their inherent limitations, have found wide acceptance as metrics of total and peak exposure. The new metrics (Rho, $Rho_{m,}$ $Delta_n$ and $Delta_s$) despite their limitations, would not be viewed as potential replacements for AUC and Cmax unless they show superior performance to the current metrics. On the other hand, the new metrics may eventually be useful in determining early exposure since partial AUC, the measurement used for early exposure has limitations. In the future, there may be greater application of clinical endpoints as supportive data for the approval of some generic drugs, especially if the collection of PK data is difficult or compromised by the dosage form. Therefore, evaluation of early exposure may gain importance in the generic drug approval process for certain drug classes. The possibility exists that these new metrics may provide an alternative to partial AUC for evaluating early exposure. However, before this can be realized, the bioequivalence acceptance criteria, power and accuracy for the metrics need further validation. Occasionally, the bioequivalence determination using (Rho, $Rho_{m,}$ $Delta_n$ and $Delta_s$) has contradicted that obtained using the AUC and Cmax criteria. These discrepancies must be resolved before the new metrics can be considered as candidates to measure early exposure.

INFLUENCE OF A MICROEMULSION VEHICLE ON CUTANEOUS BIOEQUIVALENCE OF A LIPOPHILIC MODEL DRUG ASSESSES BY MICRODIALYSIS AND PHARMACODYNAMICS

The determination of the bioequivalence of topical products using clinical methods can be costly, time consuming and relatively insensitive. Therefore, there is interest in any methodology, which will allow the measurement of drug levels within the skin. However, there is still some uncertainty on the most appropriate layer of skin to measure drug concentrations for a given product. Therefore the information presented by the authors in this paper is of great interest to anyone doing bioequivalence studies with topical dermatologics. Microdialysis is one of many methods being investigated to measure skin drug levels.

The bioequivalence of topical dermatological dosage forms and the methods of evaluation were recently addressed in an AAPS/FDA workshop (6). Currently, for corticosteroids, a pharmacodynamic method using skin blanching is the only accepted procedure to demonstrate topical bioequivalence for a post-1962 dermatologics. All other post-1962 dermatologics require a clinical study. Although the focus of this paper is on the use of a microemulsion vehicle to enhance cutaneous absorption, its importance to the determination of bioequivalence lies mainly in the experimental methodology proposed. Following the application of topical lidocaine, the authors use microdialysis to assess drug delivery to the dermis. A pharmacodynamic (PD) procedure based upon mechanical stimulation and visual analogue scoring (VAS) is employed to evaluate pain relief. Measuring drug delivery and concurrently assessing PD response provides a new and appealing approach to determining cutaneous bioequivalence. Currently for corticosteroids conduct of a PD study alone is sufficient to determine bioequivalency. With proper validation of microdialysis, the measurement of drug delivery to the skin may become a reality and may augment current or future PD measurements. It may be possible that a single set of probes can be used to study the test and reference formulations thereby decreasing study variability. However, the relationship between bioequivalence and PD needs further investigation, as do the pharmacokinetic parameters and acceptance criteria applied to VAS. This should help to avoid disconcordant results between kinetics and dynamics especially when other PD endpoints are employed for other topical products. Other proposed PK methods currently being investigated to measure drug concentration in the local skin tissues include skin stripping, surface biopsy, and the collection of fluid from suction blisters.

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