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CRITICAL CONSIDERATIONS IN PHARMACEUTICAL BIOEQUIVALENCE TESTING

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Abstract

If two or more different dosage forms are intended to exert an identical therapeutic effect, it is essential that they have the same bioavailability. Statements regarding bioavailability and bioequivalence appear to be simple and straightforward, however, have given rise to considerable controversy in pharmaceutical and clinical circles for many years which are compounded with economic factors associated with establishing bio- and therapeutic equivalence. Many rules and regulations have been issued and equal, if not more, number of their interpretations and opinions have been reported primarily due to our insufficient understanding of the scope and depth of fundamental considerations associated with pharmaceutical bioequivalence.

The import-substituted drug product driven pharmaceutical industry in the developing countries as well as the generic drug industry should have a clear understanding of the critical considerations in pharmaceutical bioequivalence testing. In particular, the factors influencing bioavailability/bioequivalence measurements, formulation design, development and evaluation, along with study design for assessment of bioavailability and bioequivalence are pivotal to the development of a good generic product. Additionally, the intricacies associated with bioequivalence assessment of highly variable drugs, food effects in bioequivalence evaluations and the relevance of pharmacodynamics in bioequivalence studies need to be appreciated while developing a new generic product. In so doing, the resultant equivalent product will be dependable and predictable in terms of its activity, both drug release and therapeutic, thus addressing some of the contemporary issues that revolve around pharmaceutical bioequivalence.

The intention of this presentation, in addition to reviewing the fundamentals of bioequivalence, is to present a consolidated and comprehensive look at those intricacies germane to the design, development and evaluation of a pharmaceutical bioequivalent product. In particular, the following sections will be addressed: a) definition and difficulties in acceptance criteria, b) bioequivalence assessment of highly variable drugs with special emphasis on significance of reference product and single dose versus multiple dose studies, and c) superbioavailability.

Keywords: *Bioavailability, Bioequivalence, Highly variable drugs, Superbioavailability*

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I. DEFINITIONS AND DIFFICULTIES IN ACCEPTANCE CRITERIA

"Bioavailability means the rate and extent to which the active drug ingredient or the therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action." (1). We are not interested in 'absorption' per se - a measure of amount of drug which leaves the administration site and enters systemic circulation. We are interested in 'availability' of the process, i.e., how much drug in its active form is available for action.

Measurement of drug at the site of action is almost an impossible dilemma. Hence, bioavailability should be defined in terms of the site where the active ingredient, and/or metabolite(s) is measured, i.e., in biofluids such as blood, plasma, urine, etc. International Consensus statement on bioavailability and bioequivalence states: "The rate at which and the extent to which the drug substance and/or its active metabolite(s) reach(es) the systemic circulation." (2). The US-FDA Orange Books defines the concept of bioequivalence as: "Bioequivalent drug products describe the pharmaceutical equivalent products that display comparable bioavailability when studied under similar experimental conditions." Furthermore, it continues to state that, "Rate and Extent of Absorption of the test product do not show significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or, the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Where these above methods are not applicable (topically administered products for local rather than systemic effect), or other in vivo tests of bioequivalence may be appropriate."

By and large, "Two pharmaceutical products are considered to be equivalent when their bioavailabilities, from the same molar dose, are so similar that they are unlikely to produce clinically relevant differences in therapeutic and/or adverse effects." The definition of allowable difference should be made with respect to clinical relevance. Accordingly, bioequivalence criteria for every drug will be different.

Situations where bioequivalence studies are warranted include when proposed marketed dosage form is different than that used in the pivotal clinical trials. Secondly, when significant changes are implemented in the manufacture of the marketed formulation. Thirdly, when a new generic formulation is tested versus the innovator marketed product. It then becomes obvious that the same bioequivalency test may not be needed in each of these situations!

The clinicians and patients are suspect of generic products for more than one reason. There is no information provided which validates the arbitrary bioequivalence standard set by regulatory agency. Approval of a generic product has not been clinically tested in patients, whereas it is presumed that all new drugs are. It is inappropriate to assume therapeutic equivalence between two products when they are shown to be bioequivalent on in vivo and/or in vitro studies. Table 1 lists FDA review and approved NCEs during the past decade illustrating that only 38% of approved NCEs utilized the final marketed formulation in the pivotal clinical trials and 59% used a different one. (3).

Historically, the present US bioequivalence regulations were developed on not so sound scientific principles. Initial criteria permitted bioequivalency to be claimed when null hypothesis of similarity of means for extent and rate of absorption (AUC, C_{max}, T_{max}) could not be rejected at 95% confidence with the probability that a sufficient sample size had been employed so that a 20% difference is detected. This arbitrary limit was based on consultation with clinicians as to what absolute differences would be clinically acceptable (not variability or confidence limits). Bioavailability of the test product was required to be within 75% of that of the reference product in at least 75% of the subjects tested (75/75 Rule of 1977). The null-hypothesis-power rule approach led to the strategy of using the minimum sample size that would 80% power; a larger sample increased the risk of detecting an unimportant difference. The negative aspects of this approach were overcome by the adoption of the two one-sided tests procedure for bioequivalence which is the current standard. Traditionally designed bioequivalence crossover designs do not measure intra-subject variability for subjects taking the same dosage form upon repeated administration.

While Table 2 lists the various types of bioavailability/bioequivalence studies, Table 3 lists some common considerations in the study design. Table 4 lists the three primary parameters employed in establishment of bioequivalence or the lack of. While Table 5 lists the pharmacokinetic characteristics to judge the release behavior of a formulation. Tables 6 and 7 list the pharmacokinetic characteristics of single and multiple dose studies, respectively. Fig. 1 depicts the tolerance limits of bioequivalence based on current criteria and Fig. 2 depicts the truth table for bioequivalence decisions (4,5).

Table 1: Bioequivalence studies for new molecular entities approved by FDA 1/1/81-12/31/90 (Abstracted from Ref. 3)

Total NMEs approved.	220
For oral dosage administration.	97
Bioavailability requirements waived (non or minimal absorption).	3
Unavailable or insufficient date to judge.	7
Final marketed formulation same as clinical trial.	34(37.8%)
Final marketed formulation differs from that in clinical trial. (50 bioequivalence tested in vivo)	53(58.9%)

Table 2. Types of Bioavailability-Bioequivalence Studies

- Study to evaluate absolute bioavailability of a dosage form
- Dose proportionality study
- Intra/Intersubject variability study
- Dosage form(s) study
- Dosage form proportionality study
- Effect of various types of intervention studies, e.g., food, etc.
- Bioequivalence Study needed due to changes in the formulation or manufacturing process
- ANDA bioequivalence studies

Table 3. Common Considerations in Study Design

Single versus Multiple Dosing

Normal Subjects versus Patients

Monitoring Parent Drug Alone versus Drug and Metabolites

Statistical Concerns

Table 4. Parameters for Comparison in Bioequivalence Investigations

✓ Cmax (measure of rate)

✓ Tmax (measure of rate)

✓ AUC (measure of extent)

Table 5. Powerful Pharmacokinetic Characteristics to Judge the Release Behavior of any Formulation

	SINGLE DOSE	MULTIPLE DOSE
Established	AUC Ae(ur) C_{max} MRT $t_{½}$	AUCt,ss (or $C_{av,ss}$) Ae(ur) $C_{max,ss}$ $t_{½}$
Alternatives	PRF HVD τC_{av} τ_{mec} VRT	PTF HVD $\tau C_{av,ss}$ $\tau_{mec,ss}$ AUCF

Table 6. Pharmacokinetic Characteristics of Single Dose Studies

A_e	Amount of unchanged drug excreted in the urine
AUC	Area under the plasma-concentration-time curve from 0-∞
AUC_{o-t}	Area under the plasma-concentration-time curve from 0-last time
C_{av}	point
C_{max}	Average concentration expected after single dose (AUC/τ)
C_{ss}	Maximum (peak) plasma drug concentration
HVD	Concentration at the end of the expected dosing interval
K_a	Half value duration
K_{el}	Absorption rate constant (first order)
MRT	Elimination rate constant (first order)
MAT	Mean residence time
VRT	Mean absorption time
PRF	Variance in residence time
PRS	%-peak-residual-fluctuation
τC_{av}	%-peak-residual-swing
τ_{mec}	Duration above C_{av}
$t_{½}a$	Duration of the minimum effective concentration
$t_{½}$	Absorption half-life
t_{max}	Elimination half-life
t_{mec}	Time to reach peak (maximum) concentration following administration
	Time to reach minimum effective concentration

Table 7. Pharmacokinetic Characteristics of Multiple Dose Studies

$Ae_{r,ss}$	Amount of unchanged drug excreted in the urine during a dosage interval at steady state
AUCF	% - AUC fluctuation
AUC_{ratio}	Ratio of AUC during first part of dosing interval and AUC during second part of dosing interval
AUC_{r}	AUC for the dosing interval
$AUC_{r,ss}$	AUC during dosing interval at steady state
$C_{av,ss}$	Mean or average steady-state plasma drug concentration during a dosage interval
$C_{max,ss}$	Maximum (peak) steady-state plasma drug concentration during a dosage interval
$C_{min,ss}$	Minimum (trough) steady-state plasma drug concentration during a dosage interval
C_{peak}	Expected Maximum (peak) and
C_{trough}	Minimum (trough) concentration
PTF	%-peak-trough-fluctuation
PTS	%-peak-trough-swing
R_A	Accumulation ratio
$\tau C_{av,ss}$	Duration above Cav,ss
$\tau_{mec,ss}$	Duration of minimum effective concentration at steady-state

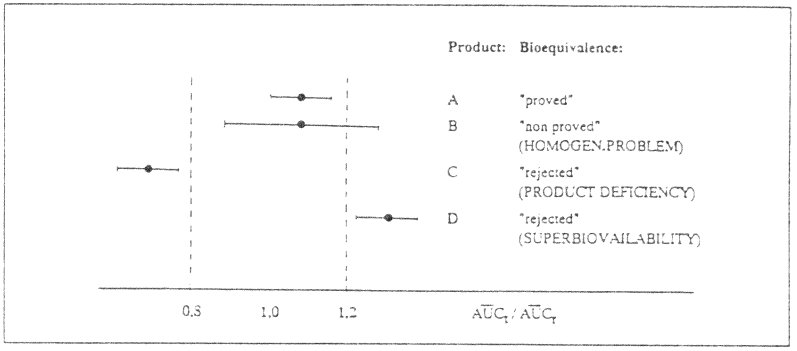

Fig. 1. Tolerance limits of bioequivalence [Ref. 4]

DECISION	TRUTH: Bioequivalent	TRUTH: Not Bioequivalent
Bioequivalent	Right Decision Everyone Gains	Wrong Decision Consumer Loses
Not Bioequivalent	Wrong Decision Sponsor Loses	Right Decision Consumer Gains

Fig. 2. Truth table for bioequivalence decisions [Ref. 5]

II. BIOEQUIVALENCE ASSESSMENT OF HIGHLY VARIABLE DRUGS

A. Significance of Reference Product

Where a bioequivalence study is required, often there is little choice concerning the reference product. European Note for Guidance on the Investigation of Bioavailability and Bioequivalence, states "Generic products are normally compared with the corresponding form of a well established 'innovator' medicinal product". Normally -- indicates that there could be (are) exceptions. Secondly, "well

established" is undefined at this point.

Highly Variable Drug is defined as a drug for which considerable differences can be found between formulations that are intended to be similar. Very often such a formulation will exhibit high within-subject (intra-subject) variability. In such cases, choice of the proper reference product can be a significant problem for highly variable drugs.

Problems from three possible sources can arise, namely, variability due to intrinsic properties of the chemical entity, variability in biopharmaceutical properties, and fragmented drug market.

Complications due to variable chemical entity could be due in part to, or a combination of poor and/or pH dependent solubility, poor stability in the GI tract, and poor GI absorption. Additionally, the drug's susceptibility to food effects, high first-pass metabolism, and non-linear pharmacokinetics can complicate the bioavailability picture. Furthermore, complications due to variable dosage forms can result in unexpected variation in bioavailabilities.

Figures 3-7 provide examples different marketed "reference" products for four drugs in Europe (6). One can appreciate the need for identifying and the appointment of one single standard reference for each of these drug entities along with, possible, their respective dissolution test conditions and criteria. Some suggestions to simplify and improve the choice of a reference product:

1. If the proposed generic product has significantly better biopharmaceutical properties than the innovator product which is biopharmaceutically "less than desirable", the proposed product on approval should be appointed as the reference product.

2. For C/MR products the reference product used in evaluations must be declared (e.g. AB rating used in the US).

3. For EC: The best available product in one of the EC countries as the single reference product for the entire EC.

b. Single- Versus Multiple-Dose Studies

Single-dose and multiple-dose studies have been routinely employed in bioavailability assessments of drugs. High pharmacokinetic variabilities are often the reasons for the therapeutic failure of positive bioequivalence investigation following single-dose application. Multiple-dose investigations, then perhaps, could be more appropriate to assess bioequivalence of such highly variable drugs. It must be noted, however, that while both single- and multiple-dose AUC data yield similar estimates of the extent of bioavailability, the peak-trough characteristics, i.e., absorption rate at steady-state cannot be predicted, based on single dose

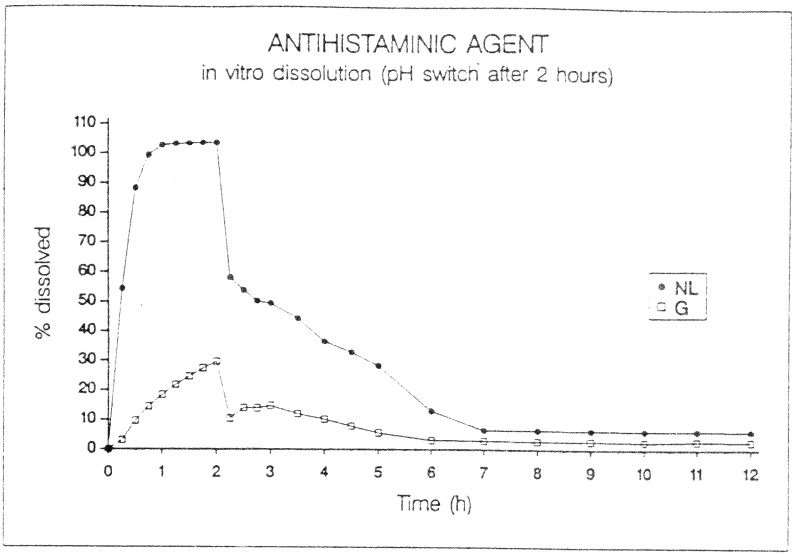

Fig. 3. Dissolution profiles of two antihistamine products marketed in The Netherlands (NL) and Germany (G) [Ref. 6]

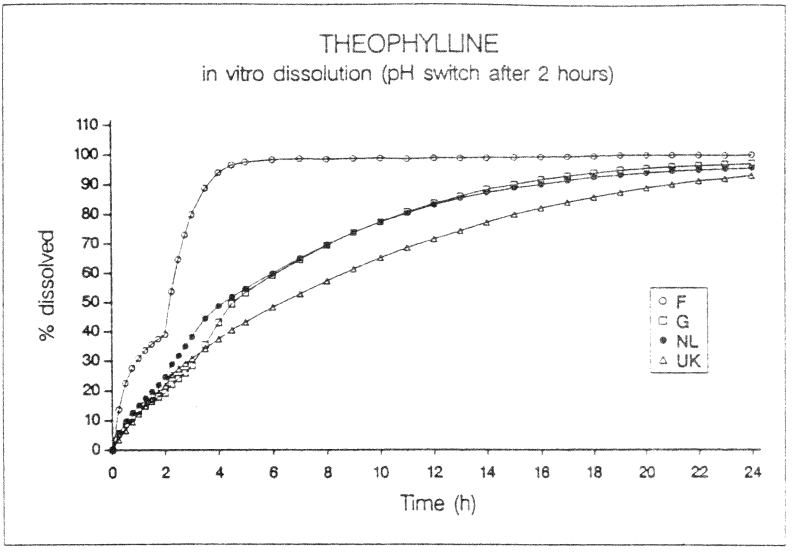

Fig. 4. Dissolution profiles of twice-daily theophylline products marketed in The Netherlands (NL), Germany (G), United Kingdom (UK) and France (F) [Ref. 6]

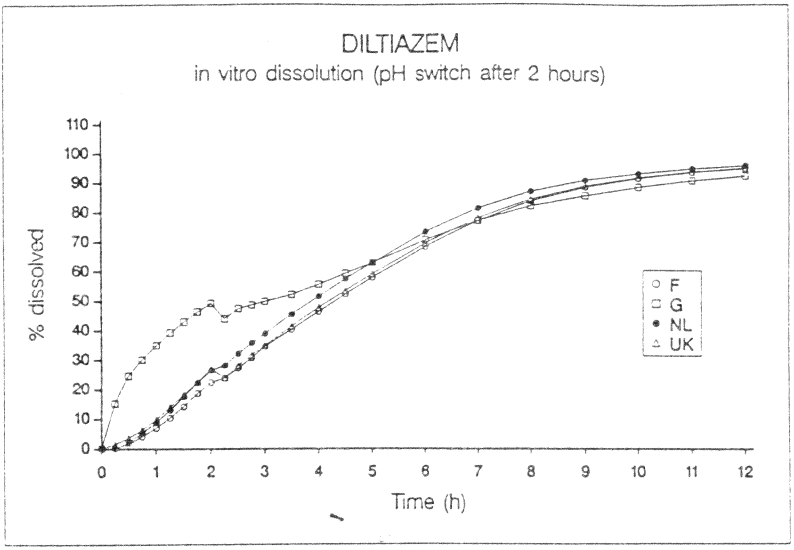

Fig. 5. Dissolution profiles of controlled release diltiazem products marketed in The Netherlands (NL), Germany (G), United Kingdom (UK) and France (F) [Ref. 6]

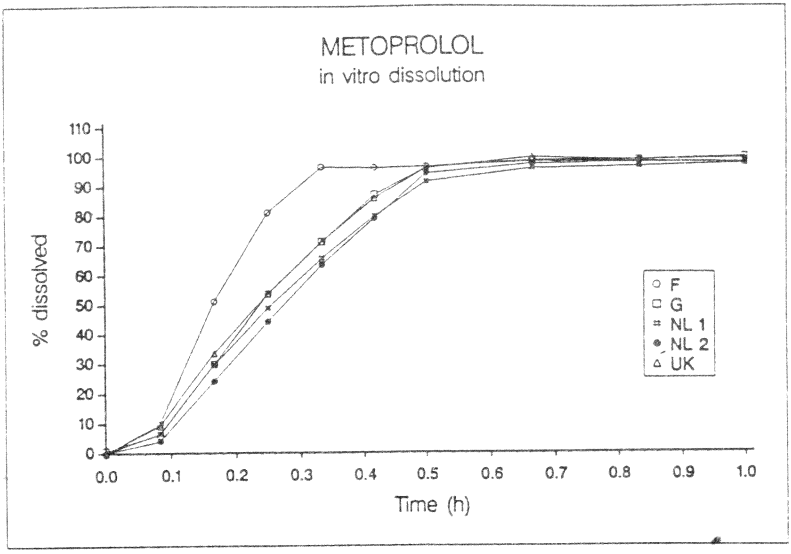

Fig. 6. Dissolution profiles of metoprolol products marketed in The Netherlands (NL), Germany (G), United Kingdom (UK and France (F) [Ref. 6]

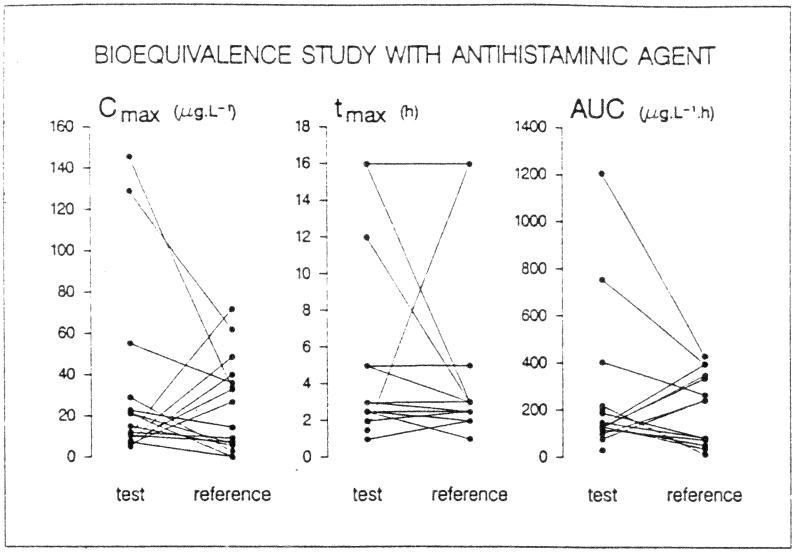

Fig. 7. Bioequivalence investigation for an antihistamine [Ref. 6]

results. Table 8 lists some of the advantages offered by multiple-dose studies.

Interindividual variability is not the primary crucial factor as long as bioequivalence studies are based on crossover studies with an intra-individual comparison of data. It is therefore important to differentiate between inter- and intrasubject variability. Pronounced intersubject variability can be observed, possibly, due to factors such as excessive first-pass metabolism, differences in extent and rate of metabolism, and other, wherein CV values exceed 40 to 50%. Table 9 lists some examples of highly variable drugs (3).

During Bio-International '89, a consensus was reached with regard to acceptable limits for intra-subject variability. The decisive limit for a 'critical' intraindividual variability was defined as 30% CV, calculated from ANOVA. Consequently, drugs which exhibit intrasubject variabilities of more than 30% are to be designated as HIGHLY VARIABLE DRUGS. Some factors that influence inter- and intra-subject variability include physiological factors, pharmacokinetic as well as physicochemical properties, drug application conditions -- route, mode, etc., and, of course formulation characteristics. Three cases are presented.

CASE I: Nifedipine: The salient features of the investigation include a single dose, 10 mg Immediate Release (IR) formulation applied to 16 healthy subjects under fasting conditions employing a crossover study design. Figures 8-10 depict the bioavailability of nifedipine, comparison of parameters between test and reference formulations and confidence limit comparisons, respectively (7).

Table 8. Advantages of Multiple-Dose Studies

Can be conducted in patients. Single-dose studies are performed in healthy subjects.
Usually smaller intersubject variability is observed in steady-state studies, which may permit use of the use of fewer subjects.
It is desirable to minimize the duration of the overall study due to potential intraindividual variability. .... accomplished in multiple-dose studies by eliminating long washout periods.
Saturable pharmacokinetics can be more readily detected at steady state following multiple-dose studies.

Table 9. Examples of highly variable drugs (from Ref. 4)

Acetylsaliclic Acid
Fluphenazine
Glycerol Trinitrate
Isosorbide Dinitrate
Loratadine
Nifedipine
Prednisone
Propafenone
Propranolol
Spironolactone
Tilidine
Verapamil

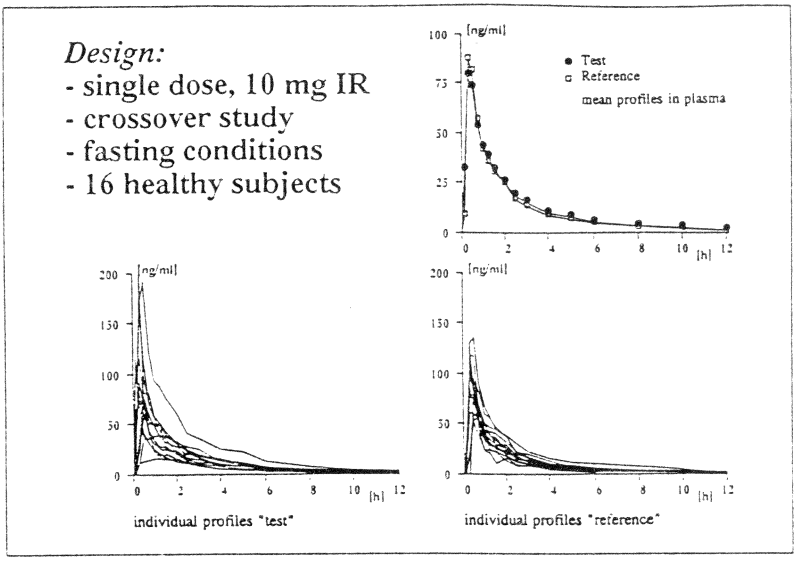

Fig. 8. Single dose bioequivalence study for nifedipine [Ref. 7]

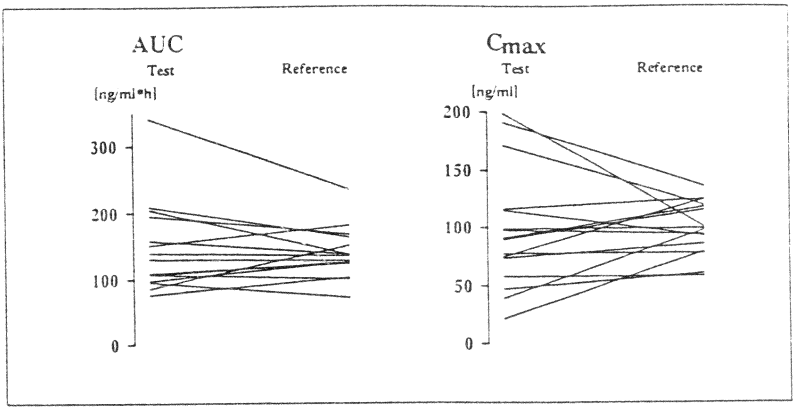

Fig. 9. Single dose bioequivalence study for nifedipine: Variation in bioequivalence parameters [Ref. 7]

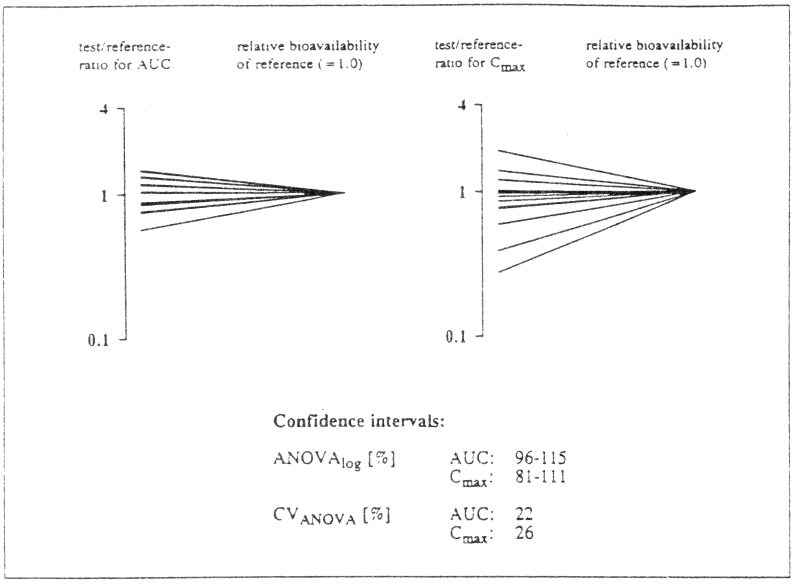

Fig. 10. Single dose bioequivalence study for nifedipine: Test:Reference ratios at 90% CI [Ref. 7]

The following observations can be drawn:

- For each subject after administration of Test and Reference product, were consistent with respect to performance
- Low CV_{ANOVA} : C_{max} 26% 81-111 Confidence interval (CI)
  AUC 22% 96-115 CI

Consequently, it can be concluded that although high interindividual variability, intraindividual variability is low. Hence, this drug cannot be classified as highly variable drug and the study is bioequivalent.

Case II: Propafenone: The salient features of the investigation include a single dose of 300 mg IR formulation applied to 12 healthy fasting subjects employing a crossover design. Figures 11 and 12 depict bioavailability profiles of the drug and comparison of parameters between test and reference formulations, respectively (8).

The following observations can be drawn:

- High between subject variability. High interindividual variation in rate and extent of bioavailability.

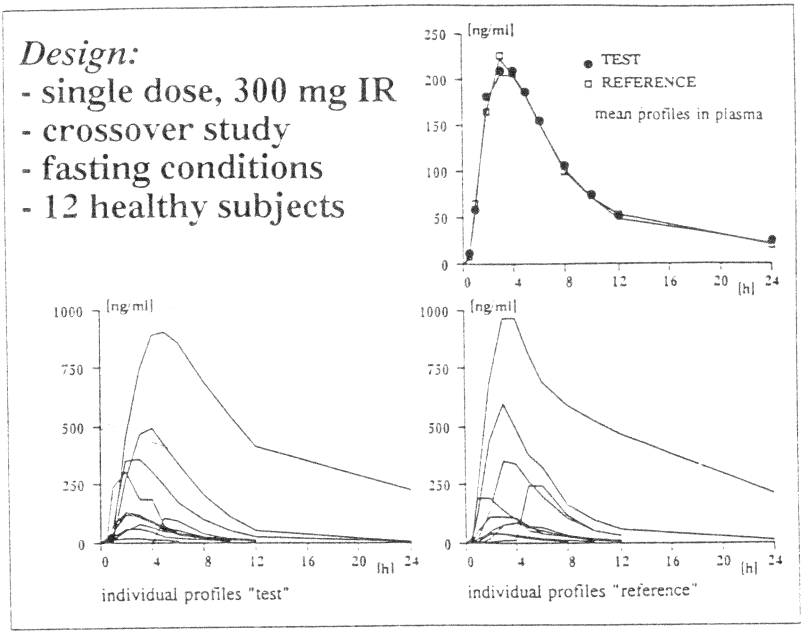

Fig. 11. Single dose bioequivalence study for propafenone [Ref. 8]

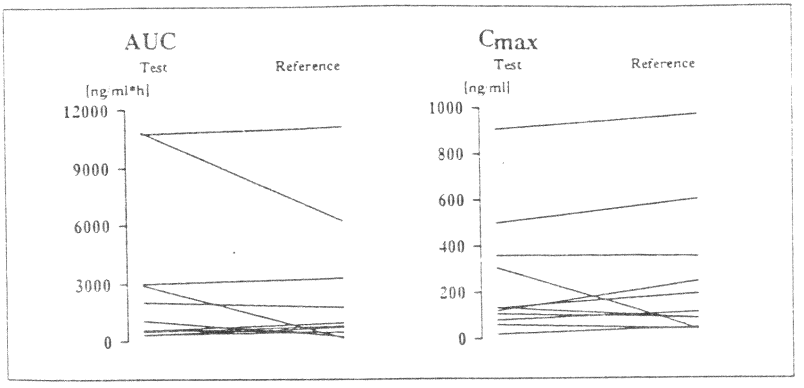

Fig. 12. Single dose bioequivalence study for propafenone: Variation in bioequivalence parameters [Ref. 8]

- High intrasubject variability in Test:Reference product ratios for C_{max} and AUC
- CV_{ANOVA} :AUC 34% 74-148 CI
  C_{max} 29% 71-160 CI

Thus, it can be concluded that propafenone can be categorized as a highly variable drug. A multiple-dose study can be recommended to address the issue of intra-subject variability.

A multiple-dose study was conducted which employed as 300 mg, twice daily dose administered to 20 healthy fasting subjects using a crossover design. Figures 13, and 14 depict the bioavailability profiles of the drug comparison of parameters between test and reference formulations (9).

Although high intersubject variability was observed, very limited intra-subject variation was evidenced. The coefficient of variations for AUC and C_{MAX} parameters were 15% and 16%, respectively, within a 90-110 confidence intervals.

Case III: Verapamil: The salient feature of this investigation include a single dose of 120 mg IR preparation administered to 18 healthy fasting subjects employing a crossover design. Figures 15 and 16 represent the drug bioavailability profiles and comparison of parameters between test and reference preparations, respectively (7). High intraindividual variability with a coefficient of variation of 31% and 32% was observed for parameters AUC and C_{MAX} with a confidence interval of 73-112. Hence, it can be concluded that veraparmil can be classified as highly variable drug. Two relative bioavailability studies, one with washout (repetitive application) and one with multiple-dose can be recommended.

A relative bioavailability study was performed with single doses of 80 mg IR preparations with wash-out period of 7 days with repetitive application to 16 healthy fasting subjects (Fig. 17). A second relative bioavailability study was conducted with repetitive application of 80 mg dose, twice daily, over 7 days to 24 healthy fasting subjects (Fig. 18, 19). The intra-subject test:reference ratios decreased significantly. The coefficient of variation using ANOVA for AUC and C_{MAX} parameters were 19% and 23%, respectively, within confidence intervals of 97-123 (7,9).

III. SUPERBIOAVAILABILITY

Interchangeability of drug-identical products without the necessity of expensive clinical studies is an aim of bioequivalence studies. 'Drug-identical products' means/include pharmaceutical equivalents, pharmaceutical alternatives and same molar doses. If the drug-identical products results in the same plasma levels one can conclude that the biological effects will be essentially the same, i.e., the drug

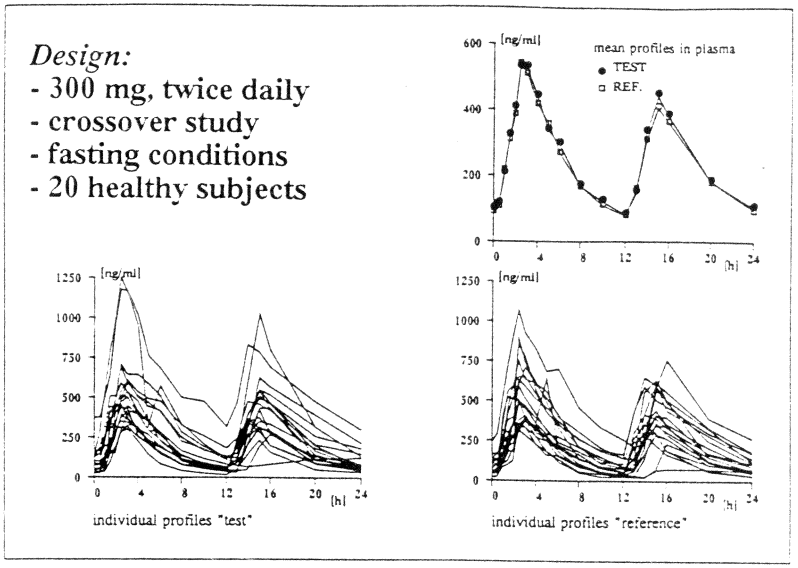

Fig. 13. Multiple dose bioequivalence study for propafenone [Ref. 9]

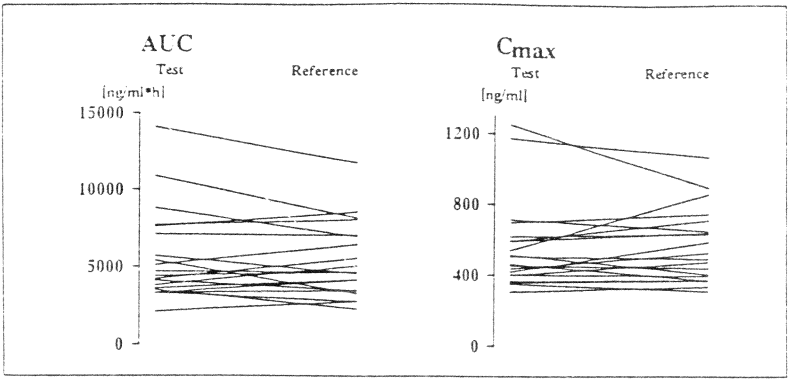

Fig. 14. Multiple dose bioequivalence study for propafenone: Variation in bioequivalence parameters [Ref. 9]

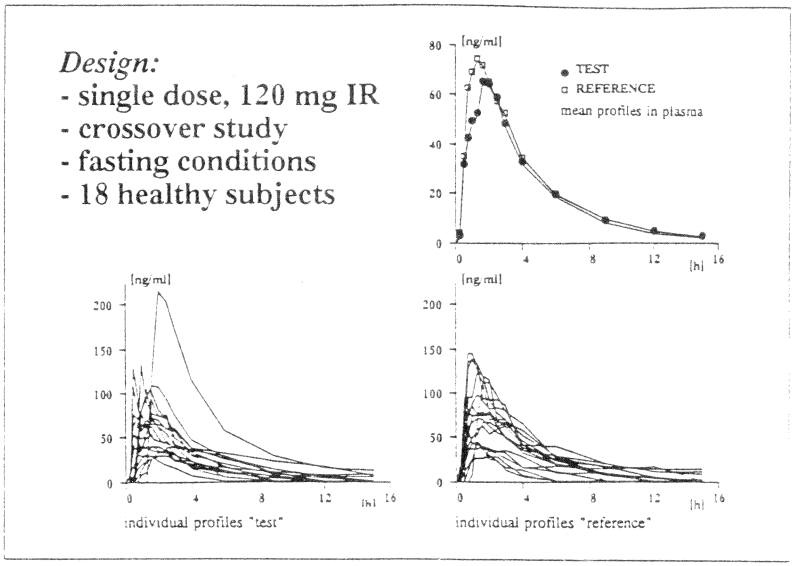

Fig. 15. Single dose bioequivalence study for verapamil [Ref. 8]

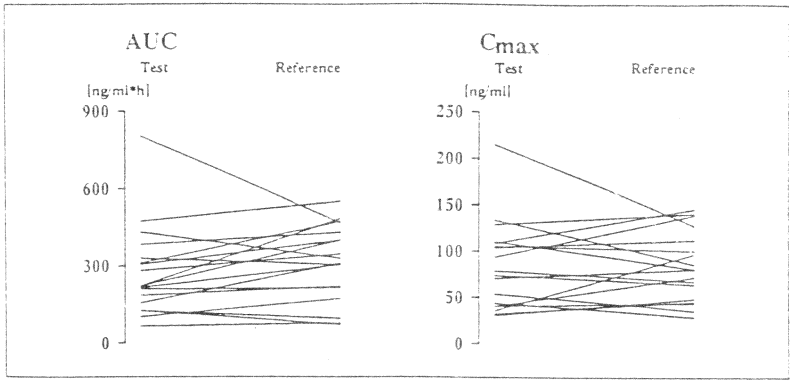

Fig. 16. Single dose bioequivalence study for verapamil: Variation in bioequivalence parameters [Ref. 8]

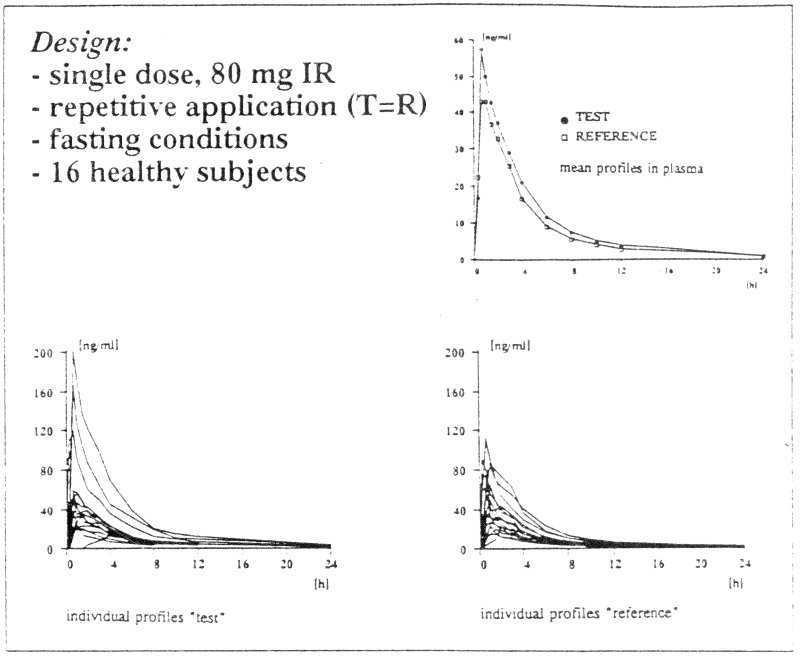

Fig. 17. Single dose with repetitive application bioequivalence study for verapamil [Ref. 8]

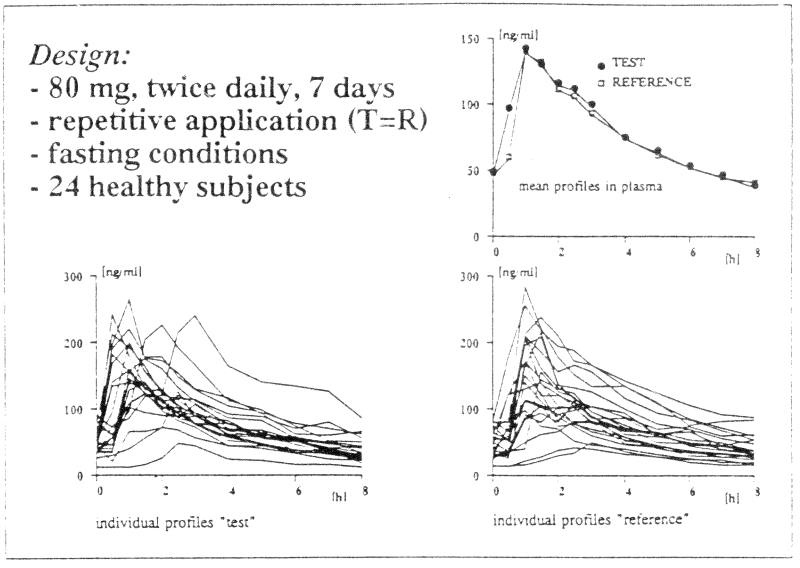

Fig. 18. Multiple dose bioequivalence study for verapamil [Ref. 9]

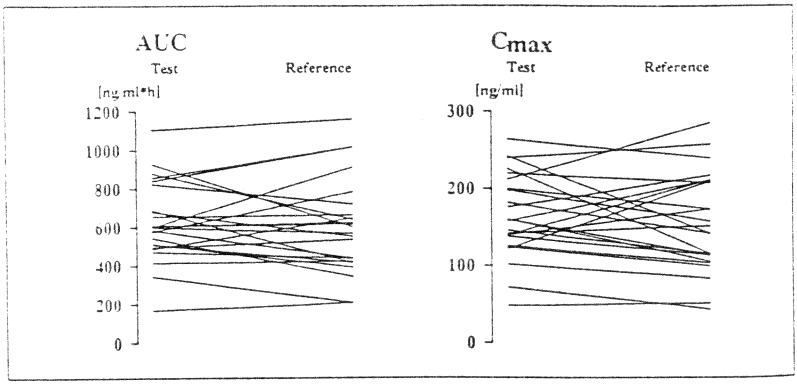

Fig. 19. Multiple dose bioequivalence study for verapamil: Variation in bioequivalence parameters [Ref. 9]

products are bioequivalent. It is assumed that the distribution of the drug substance is not influenced by the formulation.

Reasons that cause drug-identical products to yield different plasma levels under the same experimental conditions:

- chemical and physical properties of the drug substance,
- properties of the product due to excipients,
- processing,
- missing validation with resulting charge inhomogeneities.

Two fundamental reasons for different plasma levels:

- new biopharmaceutical findings -- galenical progress, and
- lack of knowledge about relevant biopharmaceutical factors.

There is dependency of the amount absorbed on the dissolution rate of the drug in conjunction with the residence time in the absorption segment of the GI tract. If dissolution rate is the rate-limiting step and the residence time is relatively short compared to the absorption half-life, then the amount of drug absorbed decreased with decreasing dissolution rate.

In the case of 'proved bioequivalence' or 'demonstrated bioequivalence', the comparative data and parameters must be within defined tolerances based on pharmacological and practical considerations. Generally, 0.8 to 1.2 limits are valid of the AUC_{test}/AUC_{ref} ratio and 0.7 to 1.3 limit for the $C_{max(test)}/C_{max(ref)}$ ratio.

The different possibilities of the area ratio and its confidence interval are shown in Fig. 1. Products A,B, and C can be appropriately accepted or rejected for bio(in)equivalence as per their position on Fig. 1. Product D is not interchangeable with the reference product has absorption greater than the upper limit and hence has to be declared bioinequivalent with reference product and rejected. Product D,

in fact, is so-called superbioavailable. In most cases enhanced extent of absorption is considered to be advantageous and the measure causing this result is the formulation package itself; it is more often referred to as galenical or product progress. However, such a statement cannot be generalized to changes in C_{max} or C_{peak} and T_{max} or T_{peak}, i.e., rate of absorption. Table 10 lists some of the drugs and drug products with potential of exhibiting superbioavailability.

Three examples will be considered in this section:

GRISEOFULVIN: A test product of micronized (average particle size 3 micron) griseofulvin was evaluated against a reference product (average particle size 20 micron - *coarse*). The AUC_{test}/AUC_{ref} ratio calculated from data reported by Atkinson [10] would have been deemed *bioinequivalent* as per current thoughts. However, all griseofulvin products on the market today contain micronized drug.

Table 10. Drug products with superbioavailability. (Abstracted from Ref. 6)

Substance	Drug Product®	Form
Cinnarizin	Cinnarizin AL75	Capsules
Cotrimoxazole	Cotrim-Puren forte	Tablets
Glyceryl trinitrate	Nitrolingual	Spray
	Nitrolingual forte	Capsules
Hydrochlorothiazide/Tria	Diuretikum Verla	Tablets
mferen	turfa	Tablets
	Iso Mack 20 mg	Tablets
Isosorbide dinitrate	Nifical	Solution
Nifedipine	Arcasin	Sirup
Phenoxymethylpenicillin	Infectocillin forte	Sirup
potassium	Meresa forte	Tablets
	Nolvadex 10	Tablets
Sulpirid	Verapamil OPT40	Sugar coated tablets
Tamoxifen	Cardioprotect 40	Sugar coated tablets
Verapamil	Verapamil-Wolff 40	Sugar coated tablets

PHENOXYMETHYL PENICILLIN SODIUM: The test product Infectocillin® (aqueous solution) which is reconstituted before use is compared with Isocillin® (oily suspension) as the reference product at the same dose level. This drug is only absorbed in the stomach and in the small intestine. The AUC_{test}/AUC_{ref} ratio of 2.2 was calculated indicating that the dissolution and/or the liberation rate of the drug from the oily vehicle of the reference product limits absorption rate. Again, as per todays standards, the test product is superbioavailable and hence *bioinequivalent*.

NITROGLYCERIN: Two chewable nitroglycerin products, Nitrolingual forte® and Perlinganit® were compared for bioequivalence. The test product exhibited higher extent of absorption due to faster drug release rate resulting in a AUC_{test}/AUC_{ref} ratio of 1.8. Once again, the products as per current requirements, will be judged *bioinequivalent* on grounds of superbioavailability.

In the three examples cited above (Table 11), the problem results from controversy between so-called "product progress" and "interchangeability of drug identical/products". Two possible solutions can be suggested.

I. Provide clinical studies for the superbioavailable test product for its registration. The cost benefit analysis, should be acceptable. Else, the manufacturer has to, on purpose, reduce the biopharmaceutical quality of the product to bring it within that of the reference product. Should the clinical studies prove to be superior to the reference then the test product will replace the reference.

II. In this solution, the term "drug identical" does not require the same molar dose, i.e., the dose of the 'superbioavailable' product could be reduced. The pharmacokinetics and the biopharmaceutical characteristics of the dosage form will decide whether the revised test product is subjected to a second bioequivalence evaluation. In case of IR formulation if the pharmacokinetics is linear and the dose is decreased isometrically (drug substance , excipients, dosage form size decreased proportionally) such a study may not be necessary. The superior pharmaceutical quality of the test product can be characterized by factor Q which is the ratio of the bioequivalent doses, which will be greater than, e.g., 1.2. Two examples are provided to illustrate this point.

Example 1: The super-bioequivalence data of two Sulprid® products whose pharmacokinetics is linear and contain a sparingly soluble drug are provided in the Table 12. The test formulation must be declared bioinequivalent since the AUC ratio is outside acceptable limits. On revision of data and isometric reduction (dose of test product reduced by 20%) the AUC ratio falls within acceptable limits and the Q factor is equal to 1.25. Thus, not only the two products are now bioequivalent, the test product also indicates better biopharmaceutical quality.

Example 2: Two liquid products of phenoxymethyl penicillin K are compared with

Table 11: Products deemed Bioinequivalent on grounds of Superbioavailability

Drug Substance	Products	AUC_I/AUC_{II}
Griseofulvin	I: 3 micron II: 20 micron	} approx. 2
Phenoxymethyl penicillin K	Infectocillin® Isocillin®	} 2.2
Nitroglycerin	Nitrolingual forte® Perlinganit®	} 1.8

regard to their bioavailability data and determined to be superbioavailable (Table 13). Applying the approach as outlined in Solution II with a dose reduction of 45% results in AUC ratio of 1.0, but the C_{max} ratio at 90% confidence interval exceeds acceptable limits. The two products are still bioinequivalent. Hence, it should be noted that Solution II is not, or may not be, a successful alternative in every instance.

CONCLUSIONS

Highly variable drugs present problems in bioequivalence assessment. For highly variable drugs, single-dose studies may not be appropriate to adequately assess intrasubject variability. Bioequivalence study of highly variable drugs require large n, preferably greater than 24. Highly variable drugs exhibit reduced intrasubject variability in steady-state. Steady-state studies are more appropriate for assessing bioequivalence of highly variable drugs.

Points to consider while developing a more appropriate bioequivalence criteria:

1. Innovator manufacturers must be required to provide both inter- and intra-subject measures of absorption rate and extent for each marketed product in the pharmacokinetic section. Such information should form the basis for defining the acceptable criteria for bioequivalence.

2. Bioequivalence studies for new products should be conducted employing a replicate design, i.e., each subject receives each treatment at least twice to reduce intrasubject variation.

Table 12. Sulpirid Products 'Bioequivalence' Data. (Abstracted from Ref. 6)

Parameters	Superbioavailability	Solution II
Tablets Meresa forte® Arminol 200R		
$Dose_r/Dose_{ref}$	1.00	0.80
AUC_r/AUC_{ref}, avg.	1.30	1.04
$C_{max(r)}/C_{max(ref)}$, avg.	1.40	1.11
90% ANOVA Confidence Interval		
AUC_{0-t}, %	119-141	95-113
C_{max}, %	116-161	93-130
$t_{max(t)} - t_{max(ref)}$, avg.	< 0.5 h	< 0.5 h
BIOEQUIVALENCE	NO	YES
$Q = Dose_{ref}/Dose_{test}$	1.00	1.25

3. New Statistical methodology be developed for evaluating item number 2, however, an upperlimit for number of subjects should be imposed.

4. Value in considering the possibility of varying the confidence interval criteria in accordance with intrasubject variability of the reference product and/or expanding bioequivalence intervals based on pharmacodynamic considerations should be explored. An appropriate design limit will be 12 X 2 repetitions per subject X 2 dosage forms resulting in no more than 48 drug administrations.

5. The basis of a standard for bioequivalency measurement for each drug should depend on inherent intrasubject variability exhibited by the drug product along with its observed pharmacokinetic/dynamic relationship.

Table 13. Phenoxymethyl penicillin K Products Bioequivalence Data (Abstrated from Ref. 4)

Parameters	Superbioavailability	Solution II
Syrup/Suspension	-	-
$Dose_{test}/Dose_{ref}$	1.00	0.45
AUC_t/AUC_{ref}, avg.	2.22	1.00
$C_{max(t)}/C_{max(ref)}$, avg.	5.00	2.25
90% ANOVA Confidence Interval		
AUC_{o-t}, %	192-252	86-113
C_{max}, %	432-620	194-280
$t_{max(t)}$-$t_{max(ref)}$, avg.	1.1 h	1.1 h
BIOEQUIVALENCE	NO	NO

REFERENCES

1. Federal Register, 42, 1648 (1977).
2. Approved Drug Products with Therapeutic Equivalence Evaluations, 11th Ed., DHHS/FDA, Center for Drug Eval. & Res., Rockville, MD (1991).
3. Benet L. Bio-International. Midha K and Blume H. (eds.) Medpharm Scientific Publishers, Stuttgart (1993).
4. Stricker H. Bio-International. Midha K and Blume H. (eds.) Medpharm Scientific Publishers, Stuttgart (1993).
5. Metzler C. Pharmaceutical Bioequivalence, Welling P., et al., (eds.) Marcel Dekker, Inc., NY (1991).
6. Oosterhuis J, et al., Controlled/Modified Release Products, Blume H, et al., (eds.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart (1991).
7. Blume H and Mutschler E. (eds.), Bioequivalenz, Govi Verlad, Frankfurt (1991).
8. Hantijarvi H. Unpublished data, Kuopio, Finland (1986).
9. Blume H. et al., Unpublished data, Eschborn, Germany (1992).
10. Atkinson R. Nat. New Biol., 193, 588 (1962).