OVERVIEW OF TEST DESIGNS

Invivo Bioequivalence Studies
Types of Studies for Immediate and Modified Release

TEST DRUG & REFERENCE DRUG

MODIFIED RELEASE

IMMEDIATE RELEASE
EXTENDED RELEASE (Controlled Release)
DELAYED RELEASE (Enteric Coated Forms)

Single Dose Study (fasting) or special conditions
Single Dose Study (food)

Single Dose Study (fasting)
Single Dose Study (food)
Multiple Dose Study (fasting)

Single Dose Study (fasting)
Single Dose Study (food)

DESIGN OF STUDY
CROSS OVER [Most Drugs]
PARALLEL [Long ½ life Drugs]

Single Dose Fasting
AUC 0 - LQC (CI)
AUC 0 - INF (CI)
C_max
T_max
λ_z (Kel)
T_1/2

Single Dose Fed
AUC 0-LQC (PE)
AUC 0-INF (PE)
C_max (PE)
T_max
λ_z (Kel)
T_1/2

Multiple Dose Fasting
AUC 0-Tau (CI)
C_max ss (CI)
C_min ss
C_ave ss
T_max
% SWING
% Fluctuation

LQC
CI
PE
AUC_0-t
AUC_0-∞
C_max
T_max
λ_z (Kel)
T_1/2
Lowest Quantifiable Concentration
90% Confidence Interval (80 - 125%)
Point Estimate (± 20%)
Area under the curve (AUC)
Area under the curve (AUC) to infinity
Maximum concentration of drug in blood
Time to maximum concentration
Terminal elimination rate constant
Time to half peak concentration

Explaining the Terms
EVALUATING TEST DATA

Statistical Bioequivalence

90% Confidence Interval

Logarithm transformed Data

TEST / REFERENCE RATIO

KEY

Bioequivalence Failure

Bioequivalence Pass

ANALYSIS OF VARIANCE

Subject : Sequence : Period : Treatment
Test & Reference Means Differences
Intra-subject Variability

STATISTICAL BIOEQUIVALENCE CRITERIA

Two One-sided Tests Procedure (α=0.05)
90% Confidence Interval (80-125%)

With acknowledgments:
Professor Laszlo Endrinyi - University of Toronto; Walter W Hauck PhD., Thomas Jefferson University. Andrew Grieve-Biometrics
Department Pfizer Central Research; Anderson and Hauck J. Pharmacokin. & Biopharm. 1990. Shein-Chung Chow & Jen-Pei Liu

Explaining the Terms

Biostudy results in these ranges favor IBE data

BOTH BIOSTUDIES PASS IBE but FAIL ABE
EXPLAINING 'THE EQUATION'

THE IBE EQUATION

EXPLAINING METRICS FOR INDIVIDUAL BIOEQUIVALENCE

Individual bioequivalence’s (IBE) basic tenet assumes that the currently employed methods and criteria for the assessment of bioequivalence are inadequate to provide assurance that the brand product can be switched to a generic product and vice versa however…

…the demands for an equivalent of the generic should not exceed those required to show equivalence of the brand itself. New requirements should be based on a demonstrated need for change or a bona fide risk and not on conjecture or theoretical supposition.

\[ (\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WT}^2 - \sigma_{WR}^2) \leq \theta_P \]

Disadvantages of using the individual approach

- Switchability will be assessed in a very small group of healthy subjects and may not reflect the extent of the problem in various groups of patients.
- How often is switchability a problem (\(\sigma_D^2\)) - relatively little evidence due to relatively few replicate studies - a possible case of "if it ain't broke don't fix it."
- Scaling with a variance term (\(\sigma_{WR}^2\)) may differ from one study to the next - aggregate/scaled criterion means that the differences in means and a significant subject by formulation interaction could be off-set by differences in the variability of the test and reference formulations - "what you lose on the swings you could gain on the roundabouts" - or vice versa.
EXPLAINING THE EQUATION

THE BIG IBE PICTURE

EXPLAINING METRICS FOR INDIVIDUAL BIOEQUIVALENCE

Individual bioequivalence (IBE) basic tenet assumes that if one were to ask a man or woman in the street what they believe is meant by approval of a generic drug as equivalent to a name-brand product... ... the answer will come back something like this, "it doesn't really matter which product I take..."

Many drugs reveal a high level of day-to-day variability of serum concentration within individuals receiving the same dose of the same brand under strictly controlled conditions... thus invalidating any existence...

\[
\left(\mu_T - \mu_R\right)^2 + \sigma_D^2 + \left(\sigma_{WT}^2 - \sigma_{WR}^2\right) \leq \theta_P
\]

Summary of individual approach

- Difference in variability between test and reference formulation have a major impact (+ or -) on the results for individual bioequivalence \((\mu_T - \mu_R)^2\)
- SIGNIFICANT DIFFERENCES in means may be off-set in differences in variability between test and reference formulations (>30%)
- These SIGNIFICANT DIFFERENCES could lead to different conclusions for average versus individual bioequivalence, thus - "what you lose on the swings you could gain on the roundabouts" - could have positive and negative implications.
- When the switchability and variance terms are very small, the IBE equation reverts to the ABE formula. Biostudy expenditure estimated to cost twice as much to establish the significance and impact of these two terms.

NEGATIVE ASPECTS

Switchability (s-b-f variation) not significant in many studies with healthy subjects

NEGATIVE ASPECTS

More variability of \(\sigma_{WR}^2\) will make it easier to pass

Scaling helps highly variable drugs (HVD) to pass the individual bioequivalence criteria

Explaining the Terms

COMPARING ABE AND IBE

Explaining the Terms

COMPARING THE DATA

WHAT YOU LOOSE ON THE SWINGS YOU GAIN ON THE ROUNDABOUTS

Three examples below of full size studies performed comparing results for individual and average bioequivalence in order to assess the importance of the different terms in the aggregate measure of individual equivalence on replicated designs. S-b-f interaction were not significant but differences in variability (+ & -) between test and reference formulations have a major impact on the results for IBE. Significant differences in means may be off-set by differences in variability between drug formulations.

STUDY 1

<table>
<thead>
<tr>
<th></th>
<th>µT</th>
<th>µR</th>
<th>σD</th>
<th>σWT</th>
<th>σWR</th>
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<tbody>
<tr>
<td>33 healthy male subjects</td>
<td>AUC</td>
<td>1.23</td>
<td>0.93</td>
<td>0.067</td>
<td>0.37</td>
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<td>Replicated study - randomized crossover</td>
<td>Cmax</td>
<td>1.13</td>
<td>0.88</td>
<td>0.073</td>
<td>0.41</td>
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<tr>
<td>Two sequences; 4 Periods (RTTR ; TRRT)</td>
<td>µT/µR</td>
<td>1.33</td>
<td>σWT/σWR</td>
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<tr>
<td>Single oral dose</td>
<td>AUC</td>
<td>1.30</td>
<td>0.93</td>
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<tr>
<td>Two week wash out between periods</td>
<td>Cmax</td>
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<td></td>
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<tr>
<td>16 blood samples taken after each dose</td>
<td>ABE</td>
<td>IBE</td>
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<tr>
<td>LC/MS validated Assay</td>
<td>90% CI P / F</td>
<td>95% UL P / F</td>
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<tr>
<td>FDA Proposed Data Analysis</td>
<td>AUC</td>
<td>1.21-1.47</td>
<td>Fail</td>
<td>1.20</td>
<td>Pass</td>
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<tr>
<td>Standard PK analysis (non-compartmental)</td>
<td>Cmax</td>
<td>1.15-1.46</td>
<td>Fail</td>
<td>1.14</td>
<td>Pass</td>
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STUDY 2

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<tr>
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<th>σWT</th>
<th>σWR</th>
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<tr>
<td>32 healthy male subjects</td>
<td>AUC</td>
<td>1673</td>
<td>1628</td>
<td>0.031</td>
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<td>Replicated study - randomized crossover</td>
<td>Cmax</td>
<td>219</td>
<td>221</td>
<td>0.099</td>
<td>0.46</td>
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<tr>
<td>Two sequences; 4 Periods (RTTR ; TRRT)</td>
<td>µT/µR</td>
<td>1.03</td>
<td>σWT/σWR</td>
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<tr>
<td>Single oral dose</td>
<td>AUC</td>
<td>0.99</td>
<td>1.53</td>
<td></td>
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<tr>
<td>Two week wash out between periods</td>
<td>Cmax</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 blood samples taken after each dose</td>
<td>ABE</td>
<td>IBE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HPLC/Fluorescence validated Assay</td>
<td>90% CI P / F</td>
<td>95% UL P / F</td>
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<tr>
<td>FDA Proposed Data Analysis</td>
<td>AUC</td>
<td>0.98-1.08</td>
<td>Pass</td>
<td>1.05</td>
<td>Pass</td>
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<td>Standard PK analysis (non-compartmental)</td>
<td>Cmax</td>
<td>0.88-1.11</td>
<td>Pass</td>
<td>2.90</td>
<td>Fail</td>
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STUDY 3

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<th>σD</th>
<th>σWT</th>
<th>σWR</th>
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<tr>
<td>40 healthy female subjects</td>
<td>AUC</td>
<td>550</td>
<td>468</td>
<td>0.021</td>
<td>0.25</td>
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<td>Replicated study - randomized crossover</td>
<td>Cmax</td>
<td>672</td>
<td>53.1</td>
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<td>1.18</td>
<td>σWT/σWR</td>
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<td>Single oral dose</td>
<td>AUC</td>
<td>1.26</td>
<td>0.73</td>
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<tr>
<td>Two week wash out between periods</td>
<td>Cmax</td>
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<td></td>
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</tr>
<tr>
<td>15 blood samples taken after each dose</td>
<td>ABE</td>
<td>IBE</td>
<td></td>
<td></td>
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<tr>
<td>GC/NPD validated Assay</td>
<td>90% CI P / F</td>
<td>95% UL P / F</td>
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<td></td>
</tr>
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<td>FDA Proposed Data Analysis</td>
<td>AUC</td>
<td>1.10-1.26</td>
<td>Fail</td>
<td>0.85</td>
<td>Pass</td>
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<tr>
<td>Standard PK analysis (non-compartmental)</td>
<td>Cmax</td>
<td>1.16-1.37</td>
<td>Fail</td>
<td>0.70</td>
<td>Pass</td>
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</table>

Data Analysis:- Log transformed AUC and Cmax

Average bioequivalence limit: 0.8-1.25
SAS PROC GLM, 90%CI using s-b-f as error

Individual bioequivalence: [Ln(1.25)/0.2]² = 1.24
SAS PROC MIXED Form,Period, Sequence, Period*sequence (form)
CSh var-cov matrix for random effects
REM estimates; CI: 2000 Bootstrap samples.

With acknowledgments Phoenix International
Explaining the Terms

The Overall Dissolution Picture

Calibrate the System FULLY

Use mild rpm conditions
Paddle 50-75 rpm
Basket 50-100 rpm

Sample every 15 minutes for IR Dosages

Perform a Comparative Dissolution Profile (4 or more points)

When both Test and Reference products dissolve 85% or more of the label amount in ≤15 minutes, a Profile Comparison is unnecessary.

USE a VALIDATED Dissolution Assay

Deaerate the dissolution medium [a critical parameter often ignored]

Compare Manual & Automatic Procedures

Dissolution Validation

Mimic the pH of the GIT Target Site

Use a Surfactant for water insoluble or sparing soluble drugs (i.e. Na lauryl sulfate)

Dissolution Performance

Evaluate the SIMILARITY Statistical Factors

Choose the right statistical Approach

Dependent Approach

Independent Approach

Dissolution Comparisons

COMPARE:
⇒ Test vs. Reference Drug Product
⇒ Bioequivalent Batch-to-Commercial Validation Lots
⇒ Pre-change to Post-Change (when a key change is made)