Scaled Average Bioequivalence: An Approach to Resolve a Difficult Program

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BIOEQUIVALENCE: USUAL REGULATORY CRITERION

Record: Parameters (AUC and Cmax) of N subjects for the Test (T) and Reference (R) products

Calculate: Averages of the logarithmic parameters for both formulations

By taking antilogs, get geometric means for the two formulations

Take the ratio (T/R) of the two geometric means (GMR)

Calculate the 90% confidence limits of GMR

Criterion: The confidence limits for GMR should be between 0.80 and 1.25.
THE PROBLEM OF HIGHLY-VARIABLE DRUGS AND DRUG PRODUCTS

**Criterion:** The confidence limits for GMR should be between 0.80 and 1.25

**Problem:** With large variation (wide confidence limits):

*it is very difficult to satisfy the regulatory criterion,*

unless the number of subjects (N) is very large

Problem especially with $C_{\text{max}}$ which often has higher variation than AUC

**Definition:** Highly-variable drug if coefficient of variation $CV \geq 30\%$
USUAL REGULATORY CRITERION: FORMALIZATION

\[ \frac{1}{\text{BEL}} \leq \text{GMR} \leq \text{BEL} \]

\text{BEL: } \text{BE limit - Usually 1.25}
\text{GMR: Ratio of geometric means}

\[ -\log(\text{BEL}) \leq \log(\text{GMR}) \leq \log(\text{BEL}) \]

\[ -\log(\text{BEL}) \leq m_T - m_R \leq \log(\text{BEL}) \]

\text{IgBEL: Logarithm of BEL}
\text{m_T, m_R: Estimated logarithmic means}
IS THERE A PROBLEM WITH BE FOR HVD/P?
MANY DRUGS PRESENTED TO FDA


Between 2003-2005:
1,010 acceptable studies
180 different drugs
57 drugs (31%) were highly variable

Note: Only acceptable studies at FDA!
With all studies,
percentage is probably higher
IS THERE A PROBLEM WITH BE FOR HVD?
FAILURE RATE OF BE STUDIES INCREASES WITH C.V.

Failing BE criteria: statistics on 1300 studies

Diane Potvin, MDS Pharma Services
IS THERE A PROBLEM WITH BE FOR HVD/P?

FAILURE RATE OF BE STUDIES INCREASES WITH C.V.

Failed BE studies (% of analytes) #

<table>
<thead>
<tr>
<th>C.V.</th>
<th>C_max Fail</th>
<th>C_max No.</th>
<th>AUC Fail</th>
<th>AUC No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-40%</td>
<td>68%</td>
<td>31</td>
<td>73%</td>
<td>22</td>
</tr>
<tr>
<td>40-45%</td>
<td>52%</td>
<td>21</td>
<td>87%</td>
<td>15</td>
</tr>
<tr>
<td>45-50%</td>
<td>87%</td>
<td>15</td>
<td>90%</td>
<td>10</td>
</tr>
<tr>
<td>50-55%</td>
<td>93%</td>
<td>14</td>
<td>100%</td>
<td>2</td>
</tr>
<tr>
<td>55-60%</td>
<td>80%</td>
<td>5</td>
<td>80%</td>
<td>5</td>
</tr>
<tr>
<td>60-65%</td>
<td>100%</td>
<td>3</td>
<td>100%</td>
<td>2</td>
</tr>
<tr>
<td>≥ 65%</td>
<td>100%</td>
<td>7</td>
<td>100%</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diane Potvin, MDS Pharma, Montréal

Failure rate is high and increases with C.V. Fewer failures for AUC than for Cmax but still a substantial number
IS THERE A PROBLEM WITH BE FOR HVD/P?
SIMILAR PRODUCTS “NOT BIOEQUIVALENT”

**A:** 2 products distinct
But small variation
“Bioequivalent”

**B:** 2 products very similar
But large variation
“Not bioequivalent”

IS THERE A PROBLEM WITH BE FOR HVD? - BIOEQUIVALENT WITH ITSELF?

Administer the same HVD formulation twice:
- generally can not demonstrate BE

Example: oral administration, on two occasions, of IsoptinSR 240 mg tablets


Lack of bioequivalence – with itself

Also: chlorpromazine formulations
POSSIBLE REDUCTION OF VARIATION USING METABOLITE DATA

Concentrations of metabolites are often less variable than of the parent drug

Simulations:
Preference depends on the contrast of intrinsic clearance and liver blood flow
G. Tucker et al., BioInternational

But: simulations considered simple assumptions (single metabolite, no subsequent metabolism)

More general conditions:
Safer to rely on data of parent drug
POSSIBLE REDUCTION OF VARIATION
STEADY-STATE STUDIES

Comparative parameters, especially of Cmax, have often (but not always) smaller variation in steady-state studies than following single oral administration.

Theoretical:


Observations:

Coefficients of variation (%)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single dose</th>
<th>Steady state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>C_max</td>
</tr>
<tr>
<td>Loratadine</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>Verapamil</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Propafenone</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>lipoic acid (R+)</td>
<td>23</td>
<td>73</td>
</tr>
<tr>
<td>lipoic acid (S+)-</td>
<td>23</td>
<td>76</td>
</tr>
</tbody>
</table>
POSSIBLE REDUCTION OF VARIATION
STEADY-STATE STUDIES

Often (but not always) lower variability

But: reduction of variability is
- Poorly defined (large, small, negative)
- Arbitrary (changes with accumulation)

Estimated $C_{\text{max}}$ has positive bias

Lower variability means reduced PK sensitivity for comparing the two drug products, diminished quality control

In Europe but not in U.S.
In Canada, for modified release (if accumulation)
DEALING WITH HIGH VARIATION:
RELAX A REGULATORY REQUIREMENT

Health Canada:

Does not require that the 90% confidence interval of the $C_{\text{max}}$ ratio be between 0.80 and 1.25

Expects only that the $C_{\text{max}}$ ratio itself should be within these limits
Dealing with High Variation:

Unscaled Average BE with Expanded Limits - Preset

Unscaled average BE:

\[
\frac{1}{BEL} \leq \text{GMR} \leq BEL
\]

- \( \log(BEL) \leq \log(\text{GMR}) \leq \log(BEL) \)
- \( \log(BEL) \leq m_T - m_R \leq \log(BEL) \)

For example:

\[
0.75 \leq \text{GMR} \leq 1.33
\]
- \( 0.288 \leq m_T - m_R \leq 0.288 \)

instead of:

\[
0.80 \leq \text{GMR} \leq 1.25
\]
- \( 0.223 \leq m_T - m_R \leq 0.223 \)

Advantage:
Simple

Disadvantage:

Arbitrary
Only partial reduction of sample size

Not for higher variabilities
DEALING WITH HIGH VARIATION:

UNSCALED AVERAGE BE WITH EXPANDED LIMITS (ABEL) - PROPORTIONAL TO ESTIMATED VARIATION

Confidence interval of log(GMR) is proportional to estimated variation:


\[ -\log BEL_S \cdot s_W \leq m_T - m_R \leq \log BEL_S \cdot s_W \]

Proportionality factor: \( \log BEL_S = 1.0 \) suggested

Advantages:
- Can apply the usual two one-sided t-tests procedure
  (However, see below)
- Statistical power is independent of sample size
- Statistical power is, with same sample size, much higher than of unscaled average BE

Comments:
- The estimated limits are random variables \( (\log BEL_S \cdot s_W) \)
- Therefore, application of the two one-sided tests procedure is not correct
  (However, approximately correct with reasonably large \( N \))
DEALING WITH HIGH VARIATION:  
SCALED AVERAGE BE (SABE)

Difference between logarithmic means is normalized by estimated variation

L. Tothfalusi et al., Pharm.Res. 18: 728-733 (2001)

\[-\text{lgBEL}_S \leq (m_T - m_R)/s_W \leq \text{lgBEL}_S\]

General procedure was suggested for setting BE limits

Advantages:
- Statistical power is independent of variation
- Statistical power is, with same sample size, much higher than of unscaled average BE
- Interpretation: Compare expected change due to switching with expected difference between replicate administrations
- Interpretation: Standardized effect size, as in clinical comparisons
**Scaled Average Bioequivalence (SABE)**

\[- \lg \text{BEL}_S \leq \frac{m_T - m_R}{s_W} \leq \lg \text{BEL}_S\]

\[
\frac{(m_T - m_R)^2}{s_W^2} \leq \lg \text{BEL}_S^2
\]

Linearizing:

\[
(m_T - m_R)^2 - \lg \text{BEL}_S^2 \cdot s_W^2 \leq 0
\]

Reject SABE if upper 95% confidence limit is positive


**Average Bioequivalence with Expanding Limits (ABEL)**

\[- \lg \text{BEL}_S \cdot s_W \leq m_T - m_R \leq \lg \text{BEL}_S \cdot s_W\]

Apply two one-sided tests procedure with the wider limits

INDIVIDUAL BIOEQUIVALENCE

Was much discussed between 1993 and 2003, and was almost adopted.

The bioequivalence model:

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

\(\mu_T\): population mean of log response to T
\(\mu_R\): population mean of log response to R
\(\sigma_D\): variance component for Subject-by-Formulation interaction
\(\sigma_{WT}\): within-subject standard deviation of log response to T
\(\sigma_{WR}\): within-subject standard deviation of log response to R

\(\sigma_W\) in the denominator:

If \(\sigma_{WR} \leq 0.294\) (\(CV_{WR} \leq 30\%\)) then \(\sigma_W = \sigma_0\), a constant

If \(\sigma_{WR} > 0.294\) (\(CV_{WR} > 30\%\)) then \(\sigma_W = \sigma_{WR}\)
Unscaled average BE if $\sigma \leq \sigma_{HV}$,

Scaled average BE if $\sigma > \sigma_{HV}$

($\sigma_{HV}$: Limiting variation)
Simulate 10,000 BE studies under each condition

Determine, at each condition, the proportion (in %) of studies in which BE is accepted: Acceptance%

Assume:
First, true bioequivalence: GMR = 1.0
Then, gradually deviate from true BE, increase GMR in steps

Plot power curve:
Acceptance% vs. GMR

Properties:
Consumer risk: Probability of accepting BE even when the two products are not equivalent
- Low level controlled by regulatory agencies

Producer risk: Probability of rejecting BE when the two products are equivalent (i.e. when GMR = 1.0)
Producer risk is independent of variability

Satisfactory producer risk with 48 subjects

Larger GMRs are permitted when variability is higher
CHARACTERISTICS OF SCALED (& UNSCALED) AVERAGE BE
N = 48, 2 PERIODS

Unscaled average BE yields low acceptance of BE with high variations

Scaled average BE does not yield low acceptance with high variations

CHARACTERISTICS OF METHODS EVALUATING BE
UNSCALED AND SCALED AVERAGE BE
PARALLEL DESIGN
N = 48

Unscaled average BE yields low acceptance of BE with high variations
Scaled average BE does not yield low acceptance with high variations
INTERPRETATIONS OF SCALED AVERAGE BIOEQUIVALENCE

**Equivalence test for effect sizes**

Standard/standardized effect size

\[(m_A - m_B)/s\]

used in medicine, psychology, quality control, etc.

**Therapeutic switchability**

Individual BE characterized switchability within subjects.

IBE reduces to SABE under some conditions.
3-period, reference-replicated design (at least)  
TRR, RTR, RRT  

HV drugs: Reference within-subject variation:  
CV > 30%  

Both AUC and $C_{\text{max}}$  

Analysis by scaled average BE (SABE)  

Acceptance criterion 1:  
$$\ln \text{BEL} = \ln(1.25)/\sigma_{W0}$$  
$$\sigma_{W0} = 0.25$$ (regulatory constant)  

Acceptance criterion 2:  
Point estimate of GMR should be between 0.80 and 1.25
SOME OUTSTANDING ISSUES: REGULATORY CONSTANT

Acceptance criterion 1

Mixed model of BE

A: Regulatory constant $CV_0 = 30\%$
B: Regulatory constant $CV_0 = 25\%$

Regulatory limits:
- Continuous with $CV_0 = 30\%$
- Discontinuous with $CV_0 = 25\%$
SOME OUTSTANDING ISSUES:
REGULATORY CONSTANT

Acceptance criterion 1:
\[ \lg \text{BEL} = \frac{\ln(1.25)}{\sigma_{W0}} \]
\[ \sigma_{W0} = 0.25 \quad \text{(regulatory constant)} \]

Regulatory constant is different
from CV = 30% (defining HV drugs)

Consequence: discontinuity

<table>
<thead>
<tr>
<th>Mixed strategy</th>
<th>Regulatory var'n (%)</th>
<th>Unscaled ABE (%)</th>
<th>Scaled ABE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>30</td>
<td>4.95</td>
<td>5.56</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>4.98</td>
<td>16.50</td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>5.01</td>
<td>6.98</td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>4.94</td>
<td>14.78</td>
</tr>
</tbody>
</table>

High consumer risk is possible

Also: Regulatory uncertainty (decision on acceptance or rejection) is enhanced

SOME OUTSTANDING ISSUES:
REGULATORY CONSTANT

\[ \sigma_0 = 0.25 \]
- Discontinuity in acceptance
  - Regulatory uncertainty
- Higher CV\(_w\) results in higher acceptance
  - Anomalous

\[ \sigma_0 = 0.294 \]
- Continuity in acceptance
  - No regulatory uncertainty
**SOME OUTSTANDING ISSUES:**

**REGULATORY CONSTANT**

Acceptance criterion 1:
\[
\lg\text{BEL} = \frac{\ln(1.25)}{\sigma_{\text{W0}}} \\
\sigma_{\text{W0}} = 0.25 \quad \text{(regulatory constant)}
\]

Consequence: **Point estimate of GMR can dominate**

---

**Joint criterion:**

Always lower than either of the component criteria

- **At low variation:** similar to Scaled ABE
- **Confidence interval criterion**
- **At high variation:** similar to Point estimate

**Joint criterion ~ Point estimate criterion**
SOME OUTSTANDING ISSUES: REGULATORY CONSTANT

\[ \lg \text{BEL} = \frac{\ln(1.25)}{\sigma_{W0}} \]

\[ \sigma_{W0} = 0.294 \]  (regulatory constant)

CV\(_0\) = 30%, GMR limit = 1.25

Joint criterion:
Low variation: almost identical to Scaled ABE
Confidence interval criterion
High variation: still fairly similar to Scaled ABE, especially at not high GMR
Joint criterion ~ Still confidence interval criterion

SOME OUTSTANDING ISSUES:
CONSTRAINT ON GMR
(Acceptance criterion 2)

Concern about possibly large deviations between estimated logarithmic means
[i.e., about log(GMR)]


Concern about interpretation to physicians & patients
SOME OUTSTANDING ISSUES: CONSTRAINT ON GMR

Larger deviation between the (logarithmic) means arises as a natural, direct consequence of the higher variability.

Larger deviations occur at higher variations.

They would be truncated by GMR constraint.

Confidence interval of log(GMR), assuming normal distribution, would not be correct.

Proposals of GMR constraints with levelling-off properties

SOME OUTSTANDING ISSUES: DETERMINATION OF $S_{WR}$

From observed data

FDA (Haidar et al., 2008)

For a given reference product, differing estimates for each test product

Awkward, especially with regulatory uncertainty

Pooled information from all available data

Preferable
SOME OUTSTANDING ISSUES:

- STUDY DESIGN

An additional goal:
To compare within-subject variations of the two drug products:

\[ s_{WT} / s_{WR} \]

Could identify highly variable drug products

Replications of both RR and TT are required

For example:

RRT
TTR
SOME OUTSTANDING ISSUES:  
- STUDY DESIGN

Refine the additional goal: To compare variations of the two drug products: \( s_{WT}/s_{WR} \) within the same subject

More effective identification of highly-variable drug products
Also: can identify (some) outlying observations

Example of study design:

RTRT
TRTR
SOME OUTSTANDING ISSUES:

- BASIS OF $s_W$

- Specific to the study
  Justified in the protocol

- From all available information
  Same for all products of a drug
  (Not modified release,
   not special preparations)
Guideline on Bioequivalence (2010):

- **Average BE with expanding limits (ABEL)**

- Only up to CV = 50%
  
  Beyond 50%:
  BE limits 70% to 143%

- **Only $C_{\text{max}}$**

- **Constraint on GMR:**
  
  Between 80% and 125%

- **Replicate design**
  
  3 or 4 periods
Advisory Committee (2004), Draft Guidance (2010): “BE for highly-variable drugs is not an issue”

[Perhaps because for $C_{\text{max}}$ only the ratio of geometric means needs to be between 0.80-1.25 ]

TPD is reconsidering the issue

(E. Ormsby, 2008, 2009)
- Expanding BE limits (ABEL)
- AUC only
- $s_w$ based on all available information
Either scaled average BE (SABE)
or average BE with expanding limits (ABEL)

$C_{\text{max}}$ only

BE FOR HIGHLY VARIABLE DRUGS: 3 REGULATORY AUTHORITIES

PARALLEL BUT SEPARATE CONSIDERATIONS

DIFFERING REGULATORY RULES!
CONCLUSIONS

1. Evaluation of bioequivalence for HV drugs has been a difficult issue for many years.

2. Major regulatory agencies are moving towards the resolution of the problem. However, the considerations are very different; no thought appears to be given to harmonization.