Reference-Scaled Average Bioequivalence (NTIDs)

Biostatistics
Reference-Scaled Average Bioequivalence (Part II: NTIDs)

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BEBAC

Low variability

Conventional concept of BE:

Two formulations with a large difference in means are declared bioequivalent if variances are low.

Modified from Fig. 1 Tothfálsúi et al. (2009)
NTIDs might be problematic

steep/flat PK/PD-curves

respond. × 2

centr. × 2

response × 20

centr. × 2
## NTIDs (FDA)

- NTIDs from ANDAs reviewed by FDA/OGD within 1996 – 2008 (89 studies)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>$AUC_{0-t}$</th>
<th>$C_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>29</td>
<td>5.7</td>
<td>12.7</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>9</td>
<td>9.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>15</td>
<td>8.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>16</td>
<td>7.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5</td>
<td>21.7</td>
<td>21.0</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>12</td>
<td>9.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Theophylline</td>
<td>3</td>
<td>17.9</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**LX Yu**  
*Approaches to Demonstrate Bioequivalence Critical Dose Drugs*  
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, April 13, 2010  
NTID\(\text{s (FDA)}\)

- For NTIDs 20\% fluctuation in plasma concentrations might be clinically relevant.
- NTIDs often have low variability; CIs of two generics might be 85–90\% and 115–120\%.

Switchability? Potential Approaches:

- AUC: PE \(\subset 90–111\%\)
- AUC: PE \(\subset 95–105\%\)
- AUC: CI \(\subset 90–111\%\) (like EMA)
- AUC: CI \(\subset 90–111\%\) and includes 100\% (like Denmark)
- AUC: CI \(\subset 95–105\%\)
- Reference Scaled Average Bioequivalence (RSABE)
NTIDs (FDA)

- Percentage of ANDAs passing tighter criteria (89 studies)

<table>
<thead>
<tr>
<th>Method</th>
<th>$AUC_{0-t}$</th>
<th>$C_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI includes 100%</td>
<td>84.3</td>
<td>69.7</td>
</tr>
<tr>
<td>CI $\subset$ 90–111%</td>
<td>86.5</td>
<td>60.7</td>
</tr>
<tr>
<td>CI $\subset$ 90–111% and includes 100%</td>
<td>77.5</td>
<td>50.6</td>
</tr>
<tr>
<td>PE $\subset$ 90–111%</td>
<td>100.0</td>
<td>95.5</td>
</tr>
<tr>
<td>RSABE</td>
<td>not assessed</td>
<td></td>
</tr>
</tbody>
</table>

- Tighter AR ensures smaller differences in mean BA
- Differences in variability between products are not addressed
- RSABE suggested

Reference: Scaled Average Bioequivalence (NTIDs)
Statistical model

- Fully replicated TRTR | RTRT design
  - ABE model
    \[-\theta_A \leq \mu_T - \mu_R \leq +\theta_A\]
  - SABE model
    \[-\theta_S \leq \frac{\mu_T - \mu_R}{\sigma_W} \leq +\theta_S\]
  - Regulatory regulatory switching condition \(\theta\) based on regulatory constant \(\sigma_0\) 0.1 and \(\Delta 1.11111 (=1/0.9, \text{the upper BE limit})\)

\[\theta \equiv \left(\frac{\ln \Delta}{\sigma_0}\right)^2\]
Evaluation

- **SABE**
  - Mixed effects model (SAS Proc MIXED, Phoenix Linear Mixed Effects).
  - Determine 95% upper confidence limit for
    \[
    \left( \bar{Y}_T - \bar{Y}_R \right)^2 - \theta \cdot s_{WR}^2
    \]
    by Howe’s method (like in SABE for HVDPs).
  - Bioequivalent if 95% upper CL ≤ 0.

- **ABE**
  - Mixed effects model.
  - Bioequivalent if 90% CI ⊂ 80.00–125.00%.
Comparison of $\sigma_{WT}$ with $\sigma_{WR}$

- Mixed effects model of intra-subject contrast $T_1-T_2$ and $R_1-R_2$ by sequence.
  
  Comparison based on $s_{WT}$ and $s_{WR}$ (the estimates of $\sigma_{WT}$ and $\sigma_{WR}$).
  
  $s_{WR}$ is already available from SABE ($R_1-R_2$); similar setup for $T_1-T_2$ to obtain $s_{WT}$.

- Determine 90% confidence interval of $\sigma_{WT}/\sigma_{WR}$ as

$$\frac{s_{WT}/s_{WR}}{\sqrt{F_{\alpha/2}(\nu_1,\nu_2)}} \leq \frac{s_{WT}/s_{WR}}{\sqrt{F_{1-\alpha/2}(\nu_1,\nu_2)}}$$
Evaluation

- Comparison of $\sigma_{WT}$ with $\sigma_{WR}$
  - $s_{WT}$ is the estimate $\sigma_{WT}$ with $\nu_1$ degrees of freedom ($\nu_1 = n_1 - 2$ in the fully replicate).
  - $s_{WR}$ is the estimate $\sigma_{WR}$ with $\nu_2$ df.
  - Probability of risk type I $\alpha = 0.1$.
  - $F_{\alpha/2(\nu_1,\nu_2)}$ is the value of the $F$-distribution with $\nu_1$ (numerator) and $\nu_2$ (denominator) degrees of freedom and a probability of $\alpha/2$.
  - $F_{1-\alpha/2(\nu_1,\nu_2)}$ is the value of the $F$-distribution with $\nu_1$ and $\nu_2$ df and a probability of $1 - \alpha/2$.
  - Bioequivalent if 95% upper CL of $\sigma_{WT}/\sigma_{WR} \leq 2.5$. 
Consequences of Scaling

- At $\sigma_{WR} 0.1 \ (CV \ 10.03\%)$ the expanded AR is $90.00-111.11\%$

<table>
<thead>
<tr>
<th>$CV_{WR}$</th>
<th>$L - U$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>94.87 – 105.41</td>
</tr>
<tr>
<td>10</td>
<td>90.02 – 111.08</td>
</tr>
<tr>
<td>15</td>
<td>85.35 – 117.02</td>
</tr>
<tr>
<td>20</td>
<td>81.17 – 123.20</td>
</tr>
<tr>
<td>25</td>
<td>77.15 – 129.62</td>
</tr>
<tr>
<td>30</td>
<td>73.40 – 136.25</td>
</tr>
</tbody>
</table>
NTIDs (FDA)

- As a consequence of scaling the AR for $s_{WR} > 0.21179$ ($CV_{WR} > 21.42\%$) will be wider than the conventional 80.00–125.00%.

- Possible ‘ways out’
  1. Cutoff on $s_{WR}$ and switch to conventional unscaled ABE
  2. A “Must Pass Both” criterion: RSABE + ABE
     - Both methods maintain the patient’s risk <5%.
       Method 2 slightly more conservative.
       Power essentially identical.

DJ Schuirmann
*Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts*
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, July 26, 2011
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommittee
forPharmaceuticalScienceandClinicalPharmacology/UCM266777.pdf
NTIDs (FDA)

- Both methods preserve the patient’s risk

DJ Schuirmann 2011

Reference-Scaled Average Bioequivalence (NTIDs)

Example

CNS drug from BEBAC’s files

- RTRT | TRTR full replicate, 18 subjects, balanced, complete
  - FDA
    1. critbound: $-0.0098283 \leq 0$ ($CV_{WR}$ 12.49%, $CV_{WT}$ 5.58%)
  - ABE: 90% CI 93.90–103.35% $\subset$ AR
  - upper 95% CL of $s_{WT}/s_{WR}$ 0.68427 $\leq 2.5$
- EMA
  - AR 90.00–111.11%
  - ABE: 90% CI 93.90–103.35% $\subset$ AR ($CV_{WR}$ 15.86%, $CV_{WT}$ 5.73%)
- Data set in Excel 2000 format:
  [http://bebac.at/downloads/NTID.xls](http://bebac.at/downloads/NTID.xls)
Example

Reference-Scaled Average Bioequivalence (NTIDs)

<table>
<thead>
<tr>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>114.00%</td>
<td>111.11%</td>
</tr>
<tr>
<td>87.72%</td>
<td>90.00%</td>
</tr>
</tbody>
</table>

Bioequivalence limits

- 80%
- 90%
- 100%
- 110%
- 120%
Thank You!

Reference-Scaled Average Bioequivalence (Part II)

Open Questions?

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References

- **ICH**
- **EMA-CPMP/CHMP/EWP**
  - Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics (2011, 2012)
- **US-FDA**
  - Center for Drug Evaluation and Research (CDER)
    - Statistical Approaches Establishing Bioequivalence (2001)
- **LX Yu**
  - Approaches to Demonstrate Bioequivalence Critical Dose Drugs
  - ACPSCP-Meeting, April 13, 2010

- **DJ Schuirmann**
  - Evaluation of Scaling Approaches to Demonstrate BE of NTI Drugs – OGD Simulation Efforts
  - ACPSCP-Meeting, July 26, 2011

- **Davit BM et al.**
  - Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration
  - The AAPS Journal 14/4, 915–24 (2012)
  - DOI: 10.1208/s12248-012-9406-x
SAS code (FDA)

Fully replicated 4-way design

```sas
data test1;
  set test;
  if (seq=1 and per=1) or (seq=2 and per=2);
  lat1t=lauct;
run;

data test2;
  set test;
  if (seq=1 and per=3) or (seq=2 and per=4);
  lat2t=lauct;
run;

data ref1;
  set ref;
  if (seq=1 and per=2) or (seq=2 and per=1);
  lat1r=lauct;
run;

data ref2;
  set ref;
  if (seq=1 and per=4) or (seq=2 and per=3);
  lat2r=lauct;
run;
```
SAS code (FDA)

Fully replicated 4-way design (cont’d)

```sas
data scavbe;
  merge test1 test2 ref1 ref2;
  by seq subj;
  ilat=0.5*(lat1t+lat2t-lat1r-lat2r);
  dlat=lat1r-lat2r;
run;

proc mixed data=scavbe;
  class seq;
  model ilat =seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=iout1;
  ods output Estimates=iout2;
  ods output NObs=iout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - ilat, mixed';
run;

pointest=exp(estimate);
x=estimate**2-stderr**2;
boundx=(max((abs(lower)),(abs(upper))))**2;
```
SAS code (FDA)

Fully replicated 4-way design (cont’d)

```sas
proc mixed data=scavbe;
  class seq;
  model dlat=seq/ddfm=satterth;
  estimate 'average' intercept 1 seq 0.5 0.5/e cl alpha=0.1;
  ods output CovParms=dout1;
  ods output Estimates=dout2;
  ods output NObs=dout3;
  title1 'scaled average BE';
  title2 'intermediate analysis - dlat, mixed';
run;

s2wr=estimate/2;
dfd=df;

theta=((log(1.11111))/0.1)**2;
y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd);
sWR=sqrt(s2wr);
critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
```

Reference-Scaled Average Bioequivalence (NTIDs)
SAS code (FDA)

Unscaled 90% BE confidence intervals

```
PROC MIXED
   data=pk;
   CLASSES SEQ SUBJ PER TRT;
   MODEL LAUCT = SEQ PER TRT/ DDFM=SATTERTH;
   RANDOM TRT/TYPE=FAO(2) SUB=SUBJ G;
   REPEATED/GRP=TRT SUB=SUBJ;
   ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
   ods output Estimates=unsc1;
   title1 'unscaled BE 90% CI - guidance version'; title2 'AUCHt';
run;
```

```
data unsc1;
   set unsc1;
   unscabe_lower=exp(lower);
   unscabe_upper=exp(upper);
run;
```

RSABE if

1. critbound \( \leq 0 \) and
2. 90% CI of ABS within 0.8000 and 1.2500 and
3. 95% upper CL of \( \frac{sWT}{sWR} \) \( \leq 2.5 \).