The FDA Approach to Bioequivalence Testing

Barbara M. Davit, Ph.D., J.D., Acting Director
Division of Bioequivalence 2, Office of Generic Drugs
Center for Drug Evaluation and Research (CDER)
United States Food and Drug Administration (US-FDA)

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The following presentation reflects the opinions of the author and does not necessarily represent the official position of the US-FDA
Outline

• The reference-scaled average bioequivalence (ABE) approach for highly variable drugs (HVDs)
• Partial AUCs (pAUCs) as a BE metric for multiphasic modified release drug products
• Implementation of the all BE studies rule
• Summary and conclusions
The reference-scaled ABE approach
Why FDA considers alternative BE approaches for HVDs

- A BE study is acceptable if the 90% confidence intervals (CIs) of the test/reference (T/R) AUC and $C_{max}$ geometric mean ratios (GMRs) are within 80-125%
- For a drug with within-subject variability ≥ 30%, it may not be possible to show BE without enrolling large numbers of subjects
- We observed that 20% of generic drugs reviewed are HVDs
Possible BE study outcomes

- Normal variability: Pass
- Low variability: Pass
- Highly variable: Fail

T/R (%)

| 80% | 125% |
How reference-scaled ABE limits differ from unscaled BE limits

<table>
<thead>
<tr>
<th></th>
<th>ABE</th>
<th>Reference-scaled ABE</th>
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<tbody>
<tr>
<td>Limits on difference</td>
<td>$-\theta_A \leq \mu_T - \mu_R \leq \theta_A$</td>
<td>$-\theta_S \leq \frac{(\mu_T - \mu_R)}{\sigma_{WR}} \leq \theta_S$</td>
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<tr>
<td>between T and R means</td>
<td></td>
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<tr>
<td>Value of $\theta$</td>
<td>$\ln(1.25)$</td>
<td>$\frac{\ln(1.25)}{\sigma_{W0}}$</td>
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</table>

FDA sets $\sigma_{WR}$ at 0.294 and $\sigma_{W0}$ at 0.25
Reference-scaled ABE studies: overall design

- Studies should use at least 24 subjects
- The Reference is given twice in the BE study
  - Either a partial replicate (3-way) or full replicate (4-way) design may be used
- The protocol should specify the intention to use the reference-scaled ABE approach
Reference-scaled ABE studies: acceptance criteria

• The 95% upper confidence bound for
  \[
  \left( \bar{Y}_T - \bar{Y}_R \right)^2 - \theta S_{WR}^2
  \]
  must be \( \leq 0 \);
  
  AND

• The GMR (point estimate) in the BE study
  must fall within 0.8 to 1.25
  
  – This is a “point estimate constraint”

  \( \hat{Y} = \ln \)-transformed AUC and \( C_{\text{max}} \) means from the BE study;
  
  \( s = \) the standard deviation from the BE study
Implied BE limits scale for HVDs, but FDA applies mixed scaling approach

We use limits of 80-125% when $s_{WR} < 0.294$

We apply scaled limits once $s_{WR} \geq 0.294$
Reference-scaled ABE: regulatory guidance

• Guidance for Industry: *BE Recommendations for Specific Products – Progesterone*
• Describes reference-scaled ABE approach
• Explains how to calculate $s_{WR}$
• Provides SAS® code for statistical analysis*
  – For 3-way, use PROC GLM
  – For 4-way, use PROC MIXED

* May use other software packages that accomplish same objectives
Acceptability of reference-scaled ABE studies in ANDAs

Based on 42 studies reviewed from 2007 to the present.

- 27 studies met scaled ABE criteria
- 2 studies failed scaled ABE criteria
- 13 studies were not acceptable for other reasons
Generic drug approvals supported by reference-scaled ABE

Three full approvals
One tentative approval
The pAUC approach
FDA proposes to use pAUC for some specialized dosage forms

• For multiphasic MR products comprised of immediate-release (IR) and delayed-release (DR) and/or extended release (ER) portions, where
  – The IR portion is necessary for rapid onset of activity;
  – The DR or ER portion is necessary to sustain activity; and
  – Due to dosing regimen, drug does not accumulate to steady-state
Proposed BE metrics for multiphasic MR products

- AUC_{0-T}
- AUC_{T-t}
- Extrapulate to AUC_\infty
- C_{max}
- T_{max}
Ritalin® LA: a candidate for pAUC approach

- Active moiety is methylphenidate (MPH)
- Formulation
  - ½ dose as IR beads
  - ½ dose as enteric-coated, DR beads
- Indicated for treatment of attention deficit disorder (ADD)
- Possible to establish a pharmacokinetic / pharmacodynamic (PK/PD) relationship between plasma concentrations and onset of response
Mean plasma profiles
Ritalin LA® qd vs IR MPH bid
PK/PD of Ritalin® LA

• Given once daily, in the morning
• Clinical outcome assessed by standardized ADD symptom rating scores
  – Score data are suitable for PD modeling
• PK / PD models show that peak response achieved at about same time as peak MPH plasma concentrations
• Response is sustained throughout the day
• MPH does not accumulate to steady-state
Proposal for pAUC BE metrics for generic versions of Ritalin® LA

• For fasting BE studies
  \[ C_{\text{max}} \quad AUC_{0-3h} \quad AUC_{3h-t} \quad AUC_\infty \]

• For fed BE studies
  \[ C_{\text{max}} \quad AUC_{0-4h} \quad AUC_{4h-t} \quad AUC_\infty \]

• AUC\textsubscript{0-3h} and AUC\textsubscript{0-4h} compare test and reference exposure associated with onset of response

• AUC\textsubscript{3h-t} and AUC\textsubscript{4h-t} compare test and reference exposure associated with sustained response
Selecting $\text{AUC}_{0-3h}$ for fasting BE studies of generics to Ritalin® LA

- In fasting subjects
  - The IR MPH $T_{\text{max}}$ [mean ± S.D.] is $2 ± 0.5 \text{ h}$;
- 2 hr is also time at which maximal response [compared to placebo] is achieved;
- By 3 hr, expect that 95% of patients should achieve maximal early onset of response
  - Mean ± 2 S.D. = 95% of population response
  - 95% of subjects should achieve maximal early onset of response by $2 \text{ h} + [2 \times 0.5 \text{ h}] = 3 \text{ h}$
Selecting AUC\textsubscript{0-4h} for fed BE studies of generics to Ritalin\textsuperscript{®} LA

- Food delays IR MPH absorption by about one (1) hour
  \(- T_{\text{max}} [\text{Mean} \pm \text{S.D.}] = 3 \pm 0.5 \text{ h}\)
- By 4 hours, expect that 95\% of subjects should achieve optimal early onset of response if MPH is taken with food
Application of the pAUC approach

• Draft guidance for BE studies of generics to Ritalin® LA was posted in November 2011
  – Second time FDA has recommended this approach

• Approach was first applied to BE studies of generic versions of Ambien CR®
  – Four generic zolpidem ER tablet products were approved using this approach
  – pAUC metrics are $\text{AUC}_{0-1.5h}$ and $\text{AUC}_{1.5h-t}$
  – pAUC sampling times were selected based on zolpidem PK/PD relationships
The all BE studies rule
The all BE studies rule: associated regulations

- Became effective July 2009
- Requires ANDA applicants to submit data from all BE studies conducted on a drug product formulation submitted for approval
The all BE studies rule: companion guidance

- Describes types of ANDA submissions covered by the All BE Studies Rule
- Recommends a format for summary reports of BE studies
- Explains types of formulations that the Agency considers to be the “same” as that submitted for approval
BE study submissions covered by the all BE studies rule

• Should submit a complete report for each BE study on which the applicant relies for approval
• Should submit a complete or summary report for all additional BE studies conducted on the same formulation of the drug product contained in
  – ANDAs
  – ANDA amendments
  – ANDA supplements requiring BE studies
  – ANDAs submitted under a suitability petition
  – ANDA annual reports
Same drug product formulation

• The formulation of the drug product submitted for approval
• Any formulations that
  – Have minor differences in composition or method of manufacture from the formulation submitted for approval
  – But similar enough to be relevant to the FDA’s determination of BE
• Examples on how to apply are given in the guidance
Calculating % differences in excipients between formulations

• Compare experimental (new) formulation versus to-be-marketed (TBM) formulation submitted for approval

• Expressed as the difference in excipient weight between the two formulations

\[
100 \times \frac{\text{amt in new formulation} - \text{amt in TBM formulation}}{\text{amt in TBM formulation}}
\]

• e.g., if new contains 105 mg filler and TBM contains 100 mg filler, this is a 5% difference
Submitting data

- Should submit a summary report for all pilot, non-pivotal, and failing BE studies on the “same” formulation as that submitted for the ANDA
  - Model Summary Tables are posted on FDA’s website
- OGD sends a deficiency letter if summary tables do not follow the format on website
- Also acceptable to submit complete report
Data on studies that fail to meet BE limits

• For an acceptable BE study, the 90% CI of the geometric mean test/reference ratios for AUC and Cmax should fall within limits of 80-125%

• For each study that fails to meet BE limits, should provide valid explanation of why this is the case

• OGD may send a deficiency if the explanation is missing or inadequate
Survey of submissions under all BE studies rule

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
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<tbody>
<tr>
<td>No. of BE submissions surveyed</td>
<td>50</td>
</tr>
<tr>
<td>Total no. of BE studies reviewed</td>
<td>199</td>
</tr>
<tr>
<td>Total no. of failed BE studies reviewed</td>
<td>88</td>
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<tr>
<td>No. of failed BE studies per submission</td>
<td>1 to 6</td>
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</table>
Information about 88 failed BE studies in survey sample

- Underpowering: 63%
- Not on final formulation: 29%
- Study design not optimal: 8%
Summary and Conclusions

• For BE studies of HVDs, applicants can reduce regulatory burden and prevent unnecessary human testing by using the reference-scaled ABE or group-sequential design approach

• FDA has begun to use pAUCs for BE studies of multiphasic MR products formulated to achieve rapid onset of response and sustained response
Summary and Conclusions (cont’d)

• FDA believes that evaluating failed BE studies will increase understanding of how changes in components, composition, and manufacturing methods may affect generic product formulation performance
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• Aaron Sigler
• Ethan Stier
• Ramana Uppoor
• Dave Vehovic
• Yannig Wang
• Lawrence Yu
References: reference-scaled ABE

- Davit et al., AAPS J 10:148-56.
- PSCPAC Meeting, 10/6/2006
- Schuirmann, GPhA Fall Technical Conference, 2008.
- PSCPAC Meeting, 8/5/2009
References: the pAUC metric

• Proposed use of pAUC as BE metric
  – FDA PSAC Meeting, 4/13/2010

• Web link for FDA Advisory Committee schedules, slides, transcripts:
  http://www.fda.gov/RegulatoryInformation/Dockets/AdvisoryCommittees/default.htm

• Zolpidem ER Tablet Draft Guidance,

• Methylphenidate ER Capsule Draft Guidance,
References: all BE studies rule

• Title 21 of the US Code of Federal Regulations
  – 21 CFR § 314.94
  – 21 CFR § 314.96
  – 21 CFR § 320.1
  – 21 CFR § 320.21

Thank you for your attention!