Scientific Considerations for Establishing Bioequivalence of Generic Drug Products

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Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA.
What is Bioequivalence (BE) ?

The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study…” [21 Code of Federal Regulation (CFR) § 320.1]

No significant difference in the rate and extent when the drug becomes available at the site of drug action
Model of Oral Dosage Form Performance Systemically Acting Drug

Dosage form performance such as dissolution

Pharmacokinetic Measurement

Drug in Solution → Gut Wall → Blood → Site of Activity → Therapeutic Effect

Clinical/PD Measurement
Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
  - “PK study”
- In vivo pharmacodynamic comparison
  - “PD study”
- In vivo limited clinical comparison
  - “Bioequivalence study with clinical endpoints”
- In vitro comparison
- Any other approach deemed appropriate by FDA
Plasma Concentration Profile

![Graph showing ln Concentration vs. Time with peaks and troughs indicating C_max and AUC](image)

- **C_max**: Maximum concentration
- **AUC**: Area Under the Curve
Therefore, BE can be pictured as:

No Better! = Safety

No Worse = Efficacy

Mean Drug Concentration in Plasma (n=34)

BE Criteria: Meet 90% CI of 80-125% for
1. Cmax
2. AUCt
3. AUCi
Components of an in vivo BE Study

- Human study
- Bioanalytical
- Statistical

Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration, March 2003
Study Design: 2-way Single Dose Crossover

Sequence I

A
Period I
Washout Period
B
Period II

Sequence II

B
Period I
Washout Period
A
Period II

A = Test Drug
B = Reference Listed Drug (RLD)
Study Design: Alternatives

- Parallel design single-dose
  - Long half-life drugs
- Replicate design single-dose
  - Highly variable drugs
PK Study Populations

- 18 years or older, healthy subjects from general population
- Why healthy subject but not patient?
  - 1). The physical processes of drug absorption are usually the same in patients as they are in healthy subjects. Healthy subjects can adequately characterize any difference in formulations
  - 2). Certain factors in patients may confound BE determination

Patients are used only when the drug is not safe to administer to healthy subjects
Single Dose vs. Multiple Dose Study Designs

- Single-Dose Design
  - Single-dose studies almost always are more sensitive

- Multiple-Dose Design
  - Multiple doses on healthy subject: safety concern
  - Multiple-dose study design is only recommended in patients who are already receiving a stable dose
PK Study Conditions

- Generally, both **Fasting and Fed** studies are recommended

- Fed study may be exempted under the following conditions for **IR product**:
  - 1). If the RLD label recommends the product to be taken on empty stomach ONLY: no fed study is needed
  - 2). If the drug product belongs to Biopharmaceutics Classification System I (BCS I) drug, BE studies may be waived (biowaiver)

- **MR Product**: Both fasting and fed BE studies are recommended

- Occasionally, **sprinkle study** is recommended if the RLD label instructed that the drug be taken in sprinkled vehicle
Parent vs. Metabolite

- Measurement of parent drug is generally recommended because the parent drug is more sensitive to the change in formulation.

- Metabolite is measured under the following two circumstances:
  1. Parent drug levels are too low to measure:
     - BE on data of metabolite
  2. Metabolite formed through pre-systemic metabolism + contributing meaningfully to the safety and efficacy of the drug product:
     - measure both parent and metabolite
     - BE on data of parent
     - metabolite data as supportive evidence
Components of in vivo BE Study

- Human Study
- Bioanalytical
- Statistical
Bioanalytical Study Considerations

Pre-study Method Validation

- Precision and Accuracy
- Linearity
- Limit of Quantitation (LOQ)
- Stability
- Selectivity

Within Study Sample Analysis:

- Detailed raw data
- Within study validation
- Reassay

Reassay is an issue!

- All reassay samples should be reassayed per an SOP that is established prior to sample analysis
- The SOP should have objective criteria for identifying samples to be reassayed
- The SOP should have objective criteria for the reporting of the reassay values
We suspect PK repeats (which we discourage) when we see the following:

- “Anomalous values”
- “Unassignable cause”
- “Incongruous values”
- “Sample reanalyzed to obtain confirming value”
- “High value between two low values”
- “Low value between two high values”
Components of in vivo BE Study

- Human Study
- Bioanalytical
- Statistical
Data Analysis

- Significantly different level is **20%**

  Two One-sided Tests Procedure:
  - (1) Test (T) is not significantly less than Ref (R)
    - 90% Confidence interval on T/R > 80%
  - (2) Ref is not significantly less than Test
    - 90% Confidence interval on R/T > 80%
    - or 90% Confidence interval on T/R < 125%

- **Bioequivalence acceptance criteria:**
  90% Confidence Interval (CI) is **80.00-125.00%** for ratio of the test/reference of three PK parameters LnAUC$_{t}$, LnAUC$_{\text{inf}}$, and LnC$_{\text{max}}$

Possible Outcome of BE Studies

- **Demonstrate BE**
- **Fail to Demonstrate BE**
- **Fail to Demonstrate BE**

T/R (%)

- 80.00%
- 125.00%
Example of Data Output

Drug A Tablets
Dose (1 x 100 mg)
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

Fasting Bioequivalence Study, Study No. 12345

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>6926.21</td>
<td>7073.05</td>
<td>0.98</td>
<td>88.52-108.32</td>
</tr>
<tr>
<td>AUC∞</td>
<td>7272.94</td>
<td>7442.56</td>
<td>0.98</td>
<td>88.79-107.55</td>
</tr>
<tr>
<td>Cmax</td>
<td>1014.78</td>
<td>1067.66</td>
<td>0.95</td>
<td>87.18-103.62</td>
</tr>
</tbody>
</table>
Can *in vivo* bioequivalence study be waived?

Yes!
Waivers of BE Study

1. The BE study can be waived for the drug products when their *in vivo* bioequivalence is self-evident

This waiver assumes that release of the drug substance from the drug product is self-evident

- Solutions: Oral/Parenteral/Inhalation/Topical
- Excipients in formulation do not affect the drug absorption
2. Waivers can be granted for the different strengths of the same product

Example:

- BE is demonstrated on the highest strength product
- The highest strength and lower strengths are proportionally similar in their formulations
- All strength products demonstrate acceptable and comparable dissolution
## Example of Formulation Proportionality

<table>
<thead>
<tr>
<th>Components</th>
<th>150 mg/tab (% w/w)</th>
<th>300 mg/tab (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>150.0 (71.94%)</td>
<td>300.0 (71.94%)</td>
</tr>
<tr>
<td>Corn Starch, NF</td>
<td>15.0 (7.19%)</td>
<td>30.0 (7.19%)</td>
</tr>
<tr>
<td>Alginic Acid, NF</td>
<td>20.0 (9.59%)</td>
<td>40.0 (9.59%)</td>
</tr>
<tr>
<td>Ethyl Cellulose, NF</td>
<td>8.0 (3.84%)</td>
<td>16.0 (3.84%)</td>
</tr>
<tr>
<td>Microcrystalline Cellulose, NF (Avicel PH-102)</td>
<td>12.5 (6.00%)</td>
<td>25.0 (6.00%)</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate, NF</td>
<td>0.5 (0.24%)</td>
<td>1.0 (0.24%)</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>2.5 (1.20%)</td>
<td>5.0 (1.20%)</td>
</tr>
<tr>
<td>Tablet tablet Weight (mg)</td>
<td>208.5</td>
<td>417.0</td>
</tr>
</tbody>
</table>
3. Waivers based on Biopharmaceutics Classification System (BCS)
What is the BCS?

- The BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability.

<table>
<thead>
<tr>
<th>Biopharmaceutics Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies For Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification system, August, 2000
BCS Biowaiver

- Drug substance is highly soluble and highly permeable (BCS 1) and is stable in the gastrointestinal tract
- The drug is not considered have a narrow therapeutic range
- Test and Reference products are pharmaceutically equivalent
- Test product exhibits rapid dissolution profile (>85% in 30 min)
- Excipients used in test product are not likely to effect drug absorption
References and Database
Product-Specific Recommendations for Generic Drug Development


- Total count 1277 as of April 2015

- First source for BE study
Common Technical Document
Summary Tables

- http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/ucm120955.htm

- These summary tables provide a standard format for data to be submitted to the Office of Generic Drugs in a concise format consistent with current recommendations.
FDA Bioequivalence Standards

- Springer 2014
- AAPS Advances in the Pharmaceutical Sciences Series
- Features a comprehensive selection: 16 chapters of the most current regulatory sciences in the bioequivalence area
- FDA scientists who themselves develop regulatory policies and conduct regulatory assessment of bioequivalence studies contributed all of the chapters