A Primer on Generic Drugs and Bioequivalence: an overview of the generic drug approval process

Division of Bioequivalence II
Reviewer
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What is a Generic Drug?

A copy of a brand-name drug, which must have the:

- same quality
- same safety
- same strength
Both brand name and generic drugs:

- are approved by the FDA
- must meet the same FDA standards for quality

Generic equivalents for a brand name drug are listed in the “Electronic Orange Book”
Myths about Generic Drugs

• Generics…are not as safe
• Generics…are not as potent
• Generics…take longer to act in the body
• Generics…are made in sub-standard manufacturing facilities
Think it’s easy becoming a generic drug in America? Think again.

FDA ensures that your generic drug is safe and effective. All generic drugs are put through a rigorous, multi-step approval process. From quality and performance to manufacturing and labeling, everything must meet FDA’s high standards. We make it tough to become a generic drug in America so it’s easy for you to feel confident.

Visit www.fda.gov/cder/ or call 1-888-INFO-FDA to learn more.

Generic Drugs: Safe. Effective. FDA Approved.

U.S. Department of Health and Human Services
FDA Legislative Support for Generic Drugs

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, made ANDAs possible by creating a compromise in the drug industry. Generic drug companies gained greater access to the market for prescription drugs, and brand-name companies gained restoration of patent life of their products lost during the FDA’s approval process.
Generic Competition

It is essential to have brand-name and generic drugs available
to meet the patient demand
to keep insurance premiums down
to save consumers $10+ billion yearly
generics represent 65% of the total prescriptions dispensed in the US
Patent Protection

A patent:
Protects the investment of the drug company that developed the brand-name drug

Gives the drug company the sole right to sell the drug while the patent is in effect
Patent Protection

When the patent on a brand-name drug nears expiration, drug companies that want to manufacture a generic can apply to the FDA to sell a generic version of the drug.
## Generic Review

<table>
<thead>
<tr>
<th>Brand Name Drug (NDA) Requirements</th>
<th>Generic Drug (ANDA) Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemistry</td>
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<tr>
<td>3. Controls</td>
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<tr>
<td>4. Labeling</td>
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<td>5. Testing</td>
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<td>7. Clinical Studies</td>
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<tr>
<td>8. Bioavailability</td>
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</table>
Generic Review Process

1. Applicant
   - ANDA
   - Acceptable and Complete?
     - Yes: Review by OGD/CDER
       - Bioequivalence Review
       - Chemistry/Micro Review
       - Request for Plant Inspection
       - Labeling Review
       - Bioequivalence Review Acceptable?
         - Yes: Preapproval Inspection Acceptable?
           - Yes: ANDA Approved
           - No: Bioequivalence Deficiency Letter
         - No: Bioequivalence Deficiency Letter
     - No: Refuse to file - letter issued
   - No: Refuse to file - letter issued
   - Chemistry/Micro Review Acceptable?
     - Yes: Not Applicable Letter
     - No: Approval deferred pending satisfactory results
   - Not Applicable Letter
The Bioequivalence Review Process
Path of Drug: From Tablet to Blood

Acidic pH

Basic pH

Metabolism?
Pathways of Drug Elimination

Drug → Blood → Liver (metabolism) → Kidney (urine) → Intestine (feces)
Definition of Bioequivalence

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 administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1
Bioequivalence

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 administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1
Rate is Essentially Measured by Cmax

• Cmax is the maximum observed concentration

• Cmax tends to have higher variability

• Need adequate sampling time-points
Cmax with Varying Absorption Rates

Effect of $ka$
kel = 0.2 hr$^{-1}$; $V = 20$ L; F•DOSE = 600 mg

- $ka = 3$ hr$^{-1}$; $t_{(peak)} = 1$ hr
- $ka = 0.6$ hr$^{-1}$; $t_{(peak)} = 2.75$ hr
- $ka = 0.125$ hr$^{-1}$; $t_{(peak)} = 6.25$ hr
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 administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1
Extent of Absorption is measured by Area Under Curve (AUC)

- **AUC_{t}** is a measure of the total exposure of drug to the body up to the last sampling time

- **AUC_{\infty}** is a theoretical measure of the total exposure of drug to the body from administration till all the drug is eliminated
Extent of absorption is Measured by Area Under Curve (AUC)

Plasma Concentration Profile of Drug X
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 administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1
Possible BE Results (90% CI)
## Example of Data Output

### Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least Squares Geometric Means</th>
<th>Ratio of Means</th>
<th>90% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>6926.21</td>
<td>7073.05</td>
<td>0.98</td>
</tr>
<tr>
<td>AUC∞</td>
<td>7272.94</td>
<td>7442.56</td>
<td>0.98</td>
</tr>
<tr>
<td>Cmax</td>
<td>1014.78</td>
<td>1067.66</td>
<td>0.95</td>
</tr>
</tbody>
</table>
General Methods for Establishing BE of Solid Oral Dosage Forms

*In Vivo*
- **Pharmacokinetic**
  - Cmax, AUCt, and AUCinf
- **Pharmacodynamic**
  - Useful when drug levels can not be measured or are not relevant

*In Vitro*
- **Dissolution**
  - Non Bio-problem drugs, non-bio strengths
- **BCS**
  - Highly permeable, Highly Soluble Drugs
How is a Pharmacokinetic (PK) BE Study Conducted?

• Study Design
  – Need a study design to allow us to assess absorption and differentiate between formulations
2-way Single Dose Crossover Design

• Two treatments:
  – single dose of test product (A)
  – single dose of RLD (B)
  – two periods
  – two sequences: AB and BA

• The subjects are randomly assigned to the sequences
2-way Single Dose Crossover Design

**Sequence I**

A → Washout Period → B

Period I

**Sequence II**

B → Washout Period → A

Period I

A = Test Drug  B = RLD
Other Designs

- **Parallel Design**
  - Treatment 1 → A → Treatment 2
  - Treatment 1 = A
  - Treatment 2 = B

- **Replicate Design**
  - 4 period (ABAB and BABA)
Types of \textit{in vivo} BE Studies

- Fasting Study

- Non-fasting (a.k.a. Fed) Study

- Sprinkled-fasting (or fed) Study
Components of in vivo BE Study

- Clinical
- Bioanalytical
- Statistical
Clinical Study Considerations

- Normal healthy subjects
  - Exception: patients
  - Male and Female
  - Racially diverse

- Strength of the test drug chosen

- Sampling time

- Protocol deviations

- Adverse event monitoring

- If fed study: high fat, high calorie breakfast
Statistical Considerations

• Subjects were included/excluded based on SOP for statistical analysis
  – Emesis
  – First non-zero concentration > 5% of its Cmax
  – Pre-dose concentration
  – Parent vs. metabolite

• 90% Confidence Interval (CI) acceptance criteria is 80.00-125.00% for the test/reference ratio for all three parameters $AUC_t$, $AUC_{\text{inf}}$, and $C_{\text{max}}$
Dissolution Testing

• Definition of dissolution
  noun: the process of going into solution; "the dissolving of salt in water" [synonym: dissolving]

• Importance of dissolution
  – Bioavailability information
  – Batch to batch consistency
  – In vitro process
Dissolution Testing (contd.)

• **Use of dissolution in Generic drugs**
  – In vitro characterization
  – Bio-waiver
  – BCS drugs

• **About dissolution testing**
  – Apparatus
  – Media
  – Volume
  – Speed
  – Time
Dissolution Testing (contd.)

• **Dissolution profile comparison**
  – Test vs. test; RLD vs. RLD
  – Different type of release products
  – Dose dumping (in different pH and alcohol)
  – $f_2$ similarity factor calculation: $f_2 \geq 50$ is considered similar

• **Setting of dissolution specifications**
  – Immediate release products
  – Delayed release products
### Dissolution Methods for Drug Products

#### Search Results for 'abacavir'

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage Form</th>
<th>USP Apparatus</th>
<th>Speed (RPMs)</th>
<th>Medium</th>
<th>Volume (mL)</th>
<th>Recommended Sampling Times (minutes)</th>
<th>Date Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Tablet</td>
<td>II (paddle)</td>
<td>75</td>
<td>0.1 N HCl</td>
<td>900</td>
<td>5, 10, 15, and 30 min</td>
<td>03/22/2006</td>
</tr>
</tbody>
</table>

[Back to Search Page](http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm)

Dissolution Methods Disclaimer

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Bio-waivers

- The cost of conducting a bioequivalence study is quite expensive
- Some drug products have several strengths
- Waivers are granted for the non-bio strengths
## Formulation Data

<table>
<thead>
<tr>
<th>Components</th>
<th>150 mg (mg/tab)</th>
<th>300 mg (mg/tab)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core Components</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active, USP</td>
<td>166.65 (71.21%)</td>
<td>333.3 (71.21%)</td>
</tr>
<tr>
<td>Ethyl Cellulose, NF</td>
<td>15.8 (6.75%)</td>
<td>31.6 (6.75%)</td>
</tr>
<tr>
<td>Alginic Acid, NF</td>
<td>20.0 (8.55%)</td>
<td>40.0 (8.55%)</td>
</tr>
<tr>
<td>Corn Starch, NF</td>
<td>8.75 (3.74%)</td>
<td>17.5 (3.74%)</td>
</tr>
<tr>
<td>Microcrystalline Cellulose, NF</td>
<td>12.5 (5.34%)</td>
<td>25.0 (5.34%)</td>
</tr>
<tr>
<td>(Avicel PH-102)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate, NF</td>
<td>0.75 (0.32%)</td>
<td>1.50 (0.32%)</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>2.55 (1.09%)</td>
<td>5.10 (1.09%)</td>
</tr>
<tr>
<td><strong>Tablet Core Weight</strong></td>
<td>227.0</td>
<td>454.0</td>
</tr>
<tr>
<td><strong>Film Coating Components</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opadry II Pink</td>
<td>6.82 (2.91%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Opadry II Red</td>
<td>N/A</td>
<td>13.61 (2.91%)</td>
</tr>
<tr>
<td>Opadry Clear</td>
<td>0.21 (0.09%)</td>
<td>0.41 (0.09%)</td>
</tr>
<tr>
<td>Purified Water USP</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Film coated tablet weight</strong></td>
<td>234.03</td>
<td>468.02</td>
</tr>
</tbody>
</table>
Dissolution Profile

Dissolution Profile of Tablet X

- % dissolved vs. Time (minutes)
- 150 mg (blue line)
- 300 mg (pink line)

f2 = 62.3
Additional Information

- www.fda.gov/cder/ogd
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Questions