Generic Drugs: What’s in a (Brand) Name
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College of Pharmacy

Disclosures
• Career Development Award – Comparative Effectiveness Research
  – K12HS019456-01
• Sedative Hypnotic use by the mentally ill: a Medicaid prescription policy study
  – Co-I: R01MH086310-03
• Consulting: Alkermes Inc.

Objectives
1. Be aware of common misconceptions about generic and brand drug equivalence
2. Summarize FDA bioequivalence standards for generic drugs to patients and other providers
3. Describe advantages of prescribing generic drugs when available
4. Be aware of strategies used to deter generic drug use

How a molecule becomes a prescription drug

Shrank W. Health Affairs, 28, no.2 (2009):546-556
Innovator Drug Patent Life

- Once new molecular entity (NME) is discovered, it is typically patented.
  - 20 year patent life
  - A new drug will only have 5-10 years of exclusivity once approved for marketing
- Prior to 1984 generic drugs were required to complete identical preclinical and clinical tests as innovator branded drugs


- Allow up to 5 extra years of patent life to innovator drugs that experience delays in FDA approval process
- Allows generic firms to file Abbreviated New Drug Applications (ANDA)
  - Must demonstrate bioequivalence to originator
  - Clinical trials of efficacy and safety NOT required
- Allows generic firms to apply for FDA approval and conduct tests of bioequivalence before the relevant patents expire
- Clarifies process for patent disputes between firms
  - 1st firm to that successfully challenges a patent granted 180 day marketing exclusivity

Intended and Unintended Consequences of Hatch-Waxman

- Generic use has soared:
  - 1000 new generics approved within 1st 2 years
  - 1984 – 18.6% of US prescriptions were generic drugs
  - 2012 - >80% of US prescriptions are dispensed as generics
- Brand drug firms game patent/legal system
  - “Ever greening” multitude of trivial patents (color, taste) – 10 per drug
  - Brand firm infringement claim triggers automatic delay of generic release for up to 30 months

NDA vs ANDA Review Process

Brand Name Drugs
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

Generic Drugs
1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

Requirements for Generic Drug Approval

1. Meet same batch requirements for identity, strength, purity, and quality
2. Be manufactured under the same strict standards of FDA good manufacturing practice regulations as for innovator product
3. Contain same active ingredient(s), same dosage, and route
4. Be therapeutically equivalent \( \Rightarrow \) bioequivalent

As number of generic products increases price is reduced

![Graph showing decrease in price as number of generic manufacturers increases](image.png)

Frank RG. NEJM. 2007;357:1993-96
Bioequivalence (BE)

The absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when two drugs are administered at the same dose, under similar conditions, in an appropriately designed study.

Meredith P. Clin Ther 2003;25:2875-90

“"I've heard that generic drugs can contain 20% less active drug than branded drugs”

NOT TRUE

Bioavailability (BA)

The measure of the rate and extent of a drug’s absorption

Bioequivalence Testing (BE)

• Prove therapeutic equivalence
• BE products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
• BE is commonly assured through two pharmacokinetic parameters
  – Cmax
  – AUC

Pharmacokinetic Profile of a Reference Drug


Comparison of PK Profiles to Determine Bioequivalence

The AUC and Cmax of the generic must meet 80% – 125% of the brand in order to be deemed BE

Typical BE Study

- 24-36 healthy subjects
- Cross-over design
  - Subjects serve as own controls with reference product
- Serial blood samples are taken over time to characterize concentrations over time
- The 90% confidence interval for ratio of Cmax and AUC between 2 tested populations must be between 80% and 125%

Generic Drug
Branded Drug

Cmax
\[ \frac{C_{max_b}}{C_{max_g}} \]
\[ \frac{AUC_b}{AUC_g} \]

Requirements for Bioequivalence

- Average difference in AUC and Cmax between branded and generic drugs (n=2070)
  - AUC: 3%
  - Cmax: 4%
  - 98% of studies - differences <10%
- This is similar to batch to batch variability of same branded drug

Application of Confidence Interval Criteria (80-125% or 0.80 - 1.25)

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand/Generic – AUC</td>
<td></td>
</tr>
<tr>
<td>Subject 1</td>
<td>1.10</td>
</tr>
<tr>
<td>Subject 2</td>
<td>1.20</td>
</tr>
<tr>
<td>Subject 3</td>
<td>1.10</td>
</tr>
<tr>
<td>Subject 4</td>
<td>1.10</td>
</tr>
<tr>
<td>Subject 5</td>
<td>0.90</td>
</tr>
<tr>
<td>Subject 6</td>
<td>1.10</td>
</tr>
<tr>
<td>Mean</td>
<td>1.10</td>
</tr>
<tr>
<td>Confidence Interval</td>
<td>0.99-1.15</td>
</tr>
<tr>
<td>Bioequivalent</td>
<td>Yes</td>
</tr>
</tbody>
</table>

FDA Requirement for Bioequivalence

Bioequivalence for Atypical Delivery Systems

- Controlled release formulations
  - Additional multiple dose trials
  - Food effects
- Locally acting drugs
  - Creams/ointments: specific to products (e.g. skin blanching for topical steroids)
  - FEV1 changes for equivalent bronchodilators

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Implications

- Average difference in AUC and Cmax between branded and generic drugs (n=2070)
  - AUC: 3%
  - Cmax: 4%
  - 98% of studies - differences <10%
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Narrow Therapeutic Index Drugs

- NTI - The range between therapeutic and toxic doses is small
- Examples: Levothyroxine, anti-epileptic drugs (phenytoin, carbamazepine, lamotrigine), warfarin, transplant drugs, lithium
- FDA bioequivalence determinations apply equally to NTI and non-NTI drugs
- Some states recognize NTI drugs as a separate category and restrict substitution

A SELECTIVE OVERVIEW OF CLINICAL EVIDENCE

"Evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs"

Kesselheim AS. JAMA 2008;300:2514-26

<table>
<thead>
<tr>
<th>Author</th>
<th>Methodology</th>
<th>Drugs</th>
<th>Association / Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zachry</td>
<td>Case-control</td>
<td>Zonisamide (42%), Gabapentin (15%), Phenytoin (14%), Clonazepam (18%), others</td>
<td>1.81 (95% CI 1.25–2.63) - ED, hospital, ambulance for epilepsy</td>
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<tr>
<td>LeLorier</td>
<td>Retrospective cohort design</td>
<td>Lamotrigine</td>
<td>1.13 (95% CI 1.09–1.18) - all outpatient visits</td>
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<tr>
<td>Rascati</td>
<td>Case-control</td>
<td>Not reported (AED)</td>
<td>1.84 (95% CI 1.44–2.36) - ED, hospital, ambulance for epilepsy</td>
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<tr>
<td>Duh</td>
<td>Retrospective cohort design</td>
<td>Topiramate</td>
<td>1.65 (95% CI 1.28–2.13) - all hospitalizations following multiple generic drug use</td>
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<tr>
<td>Andermann</td>
<td>Retrospective cohort design</td>
<td>Lamotrigine, Clobazam, Depakene</td>
<td>Healthcare utilization not assessed</td>
</tr>
<tr>
<td>Hansen</td>
<td>Case-control</td>
<td>Zonisamide (27%), Phenytoin (26%), Clonazepam (16%), CBZ (10%)</td>
<td>1.57 (95% CI 1.17–2.10) - ambulance, ED, inpatient for epilepsy</td>
</tr>
<tr>
<td>Devine</td>
<td>Case-control</td>
<td></td>
<td>1.08 (95% CI 0.91–1.29) - ED, hospital for epilepsy</td>
</tr>
<tr>
<td>Gagne</td>
<td>Case-crossover</td>
<td>Carbamazepine, Phenytoin, VPA</td>
<td>1.19 (95% 0.35–3.99)</td>
</tr>
</tbody>
</table>

Thyroid Hormone Replacement

- Turbulent history
  - BE study suppression (synthroid/levoxyl)
  - Past stability issues
- Synthetic levothyroxine (T4) became commercially available in the 50s
  - Kefauver-Harris amendment to FDCA requiring evidence of efficacy (1962)
- 1997 FDA required all T4 to receive a new NDA (2000)
- FDA has approved several AB rated generic T4 products and reformulated brands

Warfarin

Thyroid Hormone Replacement

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>AB rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthroid</td>
<td>Abbott</td>
<td>AB1, AB2</td>
</tr>
<tr>
<td>Levoxyl</td>
<td>King</td>
<td>AB1, AB3</td>
</tr>
<tr>
<td>Unitroid</td>
<td>Jerome Stevens</td>
<td>AB1, AB2, AB3</td>
</tr>
<tr>
<td>Levo-T</td>
<td>Alara</td>
<td>AB1, AB2, AB3</td>
</tr>
<tr>
<td>Levothyroxine (T4)</td>
<td>Merck</td>
<td>AB2, AB3</td>
</tr>
<tr>
<td>Levothroid</td>
<td>Lloyd</td>
<td>AB1, AB4</td>
</tr>
<tr>
<td>Levothyroxine (T4)</td>
<td>Mylan</td>
<td>AB1, AB2, AB3, AB4</td>
</tr>
<tr>
<td>Tirosint</td>
<td>Akrimax</td>
<td></td>
</tr>
</tbody>
</table>

T4 is sensitive to degradation – batch to batch variability

It is prudent to keep patients on same T4 product

We Have Entered the Golden Age of Generic Drugs

Shrank WH. Health Affairs. 2011;30:1351-57

<table>
<thead>
<tr>
<th>Expected Patent Expiration for Medications With Annual Sales Greater Than $1 Billion</th>
<th>2013-14</th>
</tr>
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<tbody>
<tr>
<td>Lumesta – 6/12</td>
<td></td>
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<tr>
<td>Actos – 8/12</td>
<td></td>
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<tr>
<td>Cymbalta – 2013</td>
<td></td>
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<tr>
<td>Lyrica − 2013</td>
<td></td>
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<tr>
<td>Vytorin – 2014</td>
<td></td>
</tr>
<tr>
<td>Celebrex – 2014</td>
<td></td>
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<tr>
<td>Lumesta Actos Cymbalta Lyrica Vytorin Celebrex</td>
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</table>

Evidence that Generic Drug Use Should Encouraged

- Generic drugs improve adherence
- Generic drugs save money for patients and other payers
- Generic drugs are typically around longer and have better safety record
  - Most new warnings occur within first 2 years of drug approval

Shrank WH. Arch Intern Med 2006;166:332-37
Shrank WH. Health Affairs 2011;30:1351-57
Shrank WH. Health Affairs 2010;29:1383-90
Strategies Used To Mitigate Patent Loss

- **Evergreening**
  - Filing patients of questionable validity that can be legally challenged and invoke additional 30 month monopoly
- **Pay for delay**
  - Financial arrangements to delay generic drug entry
- **Develop “new” molecule that has a trivial variation on original (e.g. nexium, clarinex, many XL products)**

Sue, Reformulate, Repeat...

- [Image: Figure 2. Evaluation of Abbott Laboratories' terliparatide franchise relative to generic competition.](drawing NS. Arch Intern Med 2012;Online April 9/12)

Generics, Bioequivalence, and Biosimilars....oh my

- **Biosimilars** = a biologic product that is highly similar to a previously approved biologic
  - Structural
  - Biologic functioning
- **Biosimilars Price Competition and Innovation Act (PPACA)**
  - Biologic analogue of ANDA
- 12 patent exclusivity