Brand Versus Generic Cardiac Transplant Mediations

Sallie Young, PharmD, BCPS (AQ-Cardiology)
Clinical Pharmacy Specialist, Cardiology
Penn State Hershey Medical Center
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Program Overview

- Background information
  - What is the FDA?
  - What steps do drugs go through to get approved?
  - How much does it costs to development a drug?
- Brand versus generic medications
  - What are the FDA standards?
  - Which ones are going to or have changed?
  - What does this means for the patient?
- Conclusions & Recommendations
Food & Drug Administration (FDA)

- Agency of the US Health and Human Service
- Approves all medications prior to public availability and any advisements for them, including brand and generic medications
  - Specifically evaluates safety and efficacy, appropriateness of package labeling
  - Also evaluate the manufacturer’s methods for controlling the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity

Drug Development

- Drugs may be developed from a variety of sources including:
  - Natural sources such as animals or plants
  - Human compounds such as hormones or chemicals already in our body
  - Modifications of existing compounds
- Usually tested in animals prior to humans
  - Many compounds evaluated but never tested in humans
  - 1000 compounds evaluated but only 1 makes it to trials

http://www.pharmainfo.net/reviews/drug-development-process-review
Human Clinical Trial Phases

- Phases O and I
  - Drug is given to small group of healthy volunteers (10-100), often at escalating doses
  - Effects and safety (side effects) of the compound evaluated
  - Lasts several months or more

- Phase II
  - Drug tested in a larger group of patients (several hundred) with the targeted disease
  - Evaluates safety and effectiveness of the drug
  - Lasts several months to years

http://www.pharmainfo.net/reviews/drug-development-process-review
Human Clinical Trial Phases

• Phase III
  • Further information on effectiveness and safety is obtained from studies of patients with disease
  • Up to several thousand patients may be included
  • May compare new drug to existing drugs
  • Lasts several years or more

• Phase IV
  • Continued review of approved drugs
  • Lasts as long as drug is available
Drug Development

Drugs at Each Phase

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Start</td>
<td>120</td>
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<tr>
<td>2004</td>
<td>Phase I</td>
<td>100</td>
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<tr>
<td>2005</td>
<td>Phase II</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Phase III</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>FDA approval</td>
<td>40</td>
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</tbody>
</table>

2003 – 26 drugs
2004 - 24 drugs
2005 – 26 drugs

http://www.pharmainfo.net/reviews/drug-development-process-review
New Drug Approval Process

Research

• New drug discovered & paperwork submitted to FDA
• Once patent granted, clinical trials on safety & efficacy done
• Patent typically expires 20 years from date of filing

Exclusivity

• Final approval as commercial product granted & drug available to public
• Exclusivity (marketing rights) granted by FDA – may continue past patent expiration

Generics

• After market exclusivity time over, the drug can be made by other manufacturers (called a “generic” product) if the generic company can show bioequivalence
• Application to and approval from the FDA required

Drug Development Costs

- In 2006, it was estimated to cost 500 to 2000 million dollars to bring a new drug to the market

Brand versus Generic???

Pepsi, Coca Cola

Bayer Aspirin
Brand versus Generic Products

- **Brand drug product**
  - The original formulation of a drug approved by the FDA
- **A generic drug product is**
  - “Comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use”
  - Typically, generic drugs are safe, effective, low cost alternatives to the original product
  - Generally not required to include animal & human data to establish safety and effectiveness but must demonstrate that the product is bioequivalent (i.e., performs in the same manner as the innovator drug).

Bioequivalence

- Generic medications are studied in typically 24 to 36 healthy adult volunteers
  - Amount of drug absorbed and at what time collected
- To be bioequivalent, area under curve (AUC) and maximum concentration (Cmax) must be between 80% and 125% of original product with a 90% confidence interval

Generic Products

- All generics must
  - Contain the same active ingredient as original product
    - Inactive ingredients may vary
  - Be identical in strength, dose form and route of administration
  - Be appropriately labeled
  - Meet same standards of purity and quality
  - Be manufactured under same standards as brand-name drug
Generic Products

- The generic formulation may
  - Have a different appearance
    - Vary in color, shape or size from one generic to next
  - Contain different fillers (inactive ingredients)
- Often, not all drug formulations are available
  - Liquids or IV products or different strengths sometimes are not available
Pennsylvania Law

“The pharmacist shall substitute a less expensive, generically equivalent drug unless required otherwise by the purchaser or indicated by the prescriber”
Potential Downfalls of Generics

- Generic formulations may be made in other countries
- May have different delayed release mechanisms
- May vary from one generic to another
Recent Media Stories

- 34 year old female was on Wellbutrin XL for mild depression
- Upon changing to the generic form (Budeprion XL), she experienced
  - Weight gain (15 lbs)
  - Gastrointestinal problems
  - Fatigue, lack of motivation
- Additional medications and tests were tried over next 8 months
- All symptoms disappeared within a week when she started taking Wellbutrin XL again

Recent Media Stories

- ConsumerLab.com tested Budeprion XL and found four times more active ingredient released in first 2 hours
- Attributed to the generic company using a different delayed release mechanism than brand product

Recent Media Stories

- 22 year old female hadn’t had a seizure for over 6 years while taking Trileptal
- After taking the generic for a month, she had a seizure

Recent Media Stories

- 33 year old female changed from one generic (Pliva) fluoxetine to another generic (Ranbaxy)
- Experienced relapse of her depression symptoms
- Within days of her pharmacy switching her back to Pliva generic, felt better
  - Ranbaxy was investigated by FDA who allegedly altered testing data, did not use safe manufacturing practices and used drug from unapproved sources
  - FDA stopped import of more than 30 drugs from 2 of the company’s plants

Other Generic Conversions

- For heart medications, brand-name drugs were not found to be superior to generic medications
- Included looking at studies published for
  - Beta-blockers
  - Calcium channel blockers
  - Platelet inhibitors and blood thinners (warfarin)
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Alpha-blocking medications
  - Anti-arrhythmics

Common Transplant Medications

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Purpose</th>
<th>Generic Available?</th>
<th>Generic at HMC as of July 2009?</th>
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<tbody>
<tr>
<td>Cyclosporine</td>
<td>Neoral, Gengraf</td>
<td>Anti-rejection</td>
<td>Yes</td>
<td>Yes, Gengraf and Neoral</td>
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<tr>
<td>Tacrolimus</td>
<td>Prograf</td>
<td>Anti-rejection</td>
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<td>No</td>
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<tr>
<td>Sirolimus</td>
<td>Rapamune</td>
<td>Anti-rejection</td>
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<td>No</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>Cellcept</td>
<td>Anti-rejection</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Mycophenolic acid</td>
<td>Myfortic</td>
<td>Anti-rejection</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Prednisone</td>
<td>Deltasone</td>
<td>Steroid</td>
<td>Yes</td>
<td>Yes</td>
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</table>
Advice to Patients

- Keep a list of your medications with you (and update it often!)
- Talk to your doctor, nurse and/or pharmacist about any changes in medications
- Get any laboratory tests prescribed by your healthcare provider
- Report any changes or unusual symptoms