The FDA Process for Approving Generic Drugs

Overview
- Office of Generic Drugs
- Perceptions about Generic Drugs
- New Drug vs. Generic Drug Approval Process
- Bioequivalence
- The ‘Orange Book’
Patient Perceptions

The Negatives
- Generics don't work for me
- I don't trust generics
- Why change something that is working
- I have the best insurance so I DAW my RX so I can have the best medications possible
- I read that generic drugs are not the real thing, they are not pure.
- Generics don't seem to work as well
- I am allergic to generics
- Brand name drugs taste better

The Positives
- Can we use a generic since it will not be as expensive?
- Is there a generic for drug X?
- The price has increased so much I can't afford it...
- I want to take generics whenever possible to save the healthcare system money.
- Does my medication have a generic alternative? Do you know when it will?
- Can we change to another drug that does come as a generic?

Generic Drugs
- Save an average of $53.00 for every prescription sold
- Currently save consumers $8-10 billion/year
- Significant savings to employers and health plans

And...
- Are safe and effective alternatives to brand name prescriptions
- Can help both consumers and the government reduce the cost of prescription drugs
- Are currently used in 51% of all prescriptions dispensed

Drug Price Competition and Patent Term Restoration Act of 1984
- a.k.a. Hatch-Waxman Act, amendments to the FFD&C Act
- Considered one of the most successful pieces of legislation ever passed
- Created the generic drug industry
- Increased availability of generics
  - 1984 12% prescriptions were generic
  - 2002 51% prescriptions were generic - yet only 8% of revenue for prescription drugs

Source: J.E. Billi, MD, University of Michigan Health System, October 29, 2002, “Quotes Reported by UM Physicians”
Hatch-Waxman Amendments to FFD&C Act - 1984
- Compromise legislation to benefit both brand and generic firms
- Allowed generic firms to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities (do not have to repeat expensive clinical and pre-clinical trials)
- Allowed patent extensions and exclusivities to innovator firms

What are the requirements for a generic drug product?
- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Compared to reference listed drug (RLD) - (brand name product) found in the ‘Orange Book’

What are the requirements for a generic drug application?
- Labeling
- Chemistry, Manufacturing, Controls/Microbiology
- Manufacturing Compliance
- Bioequivalence
- Legal/Regulatory

NDA vs. ANDA Review Process

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How do we assure the quality of generic drugs?
- First 5 steps of review process are identical to NDA process
- Bioequivalence for complicated products is discussed with the same staff that reviewed the brand product
- FDA has experience with the product
- Scientific literature published
- Product is known to be safe
Labeling Review

- “Same” as brand name labeling
- May delete portions of labeling protected by patent or exclusivity
- May differ in excipients, PK data and how supplied

Chemistry Review

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specs and tests
- Packaging
- Stability

Manufacturing Compliance Programs

- Purpose - To assure quality of marketed drug products
- Mechanisms - Product Testing
  - Surveillance
  - Manufacturing/Testing plant inspections
  - Assess firm’s compliance with good manufacturing processes

Definition of Bioequivalence (BE)

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

Purpose of BE Review

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner

Bioequivalence Example

![Graph showing drug concentration over time for Test/Generic and Reference/Brand](image-url)
Model of Oral Dosage Form Performance

Dosage Form Performance
- Drug in Solution
- Gut Wall
- Blood
- Site of Activity
- Therapeutic Effect

Pharmacokinetic Measurement

Clinical/PD Measurement

Plasma Concentration-Dose

Approaches to Determining Bioequivalence (21 CFR 320.24)
- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

Clinical/PD Dose-Response

Study Designs
- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed
- Alternatives
  - Single-dose, parallel, fasted
  - Single-dose, replicate design
  - Multiple-dose, two-way crossover, fasted
  - Clinical endpoint study

Waivers of In Vivo Study Requirements
- Definition
- Criteria (21 CFR 320.22)
  - In vivo bioequivalence is self-evident
  - Parenteral solutions
  - Inhalational anesthetics
  - Topical (skin) solution
  - Oral solution
  - Different proportional strength of product with demonstrated BE

Use other than as a learning aid for Pharmacotherapy Frontiers 2007 must be approved by the speaker
Statistical Analysis (Two One-sided Tests Procedure)

- AUC and Cmax
  - 90% Confidence Intervals (CI) must fit between 80%-125%
  - What does this mean?
  - Can there be a 46% difference?

Possible BE Results (90% CI)

Statistical Analysis

Evaluating Bioequivalence Results

Possible BE Results (90% CI)

Narrow Therapeutic Index (NTI) Drugs

- Drug Products that are subject to therapeutic drug concentration or pharmacodynamic monitoring
  - Examples: Digoxin, Lithium, Phenytoin, Warfarin
  - Traditional bioequivalence limit of 80-125% is unchanged for these products

In Vivo Bioequivalence Inspections

- Covers clinical and analytical components
- Objectives
  - Verify quality and integrity of the scientific data
  - Ensure rights and welfare of human subjects are protected
  - Ensure compliance with the regulations and promptly follow-up on significant problems (research misconduct; fraud)

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All FDA approved drug products listed (NDA’s, OTC’s & ANDA’s)
- Therapeutic equivalence codes
  - "A" = Substitutable
  - "B" = Inequivalent, NOT Substitutable
- Expiration dates: patent and exclusivity
- Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare with their proposed products

1984 Hatch-Waxman - gave FDA statutory authority to require a demonstration of BE before an ANDA could be approved. No longer allowed approval of bio problem drugs without an acceptable BE study.
- Products for which in vivo demonstration of BE was deferred are listed as therapeutic inequivalent or "B" rated.
- Through December 2006 approximately 2.4% of the drug products listed in the Orange Book are not rated as therapeutic, e.g. reserpine, colchicine.

Patent Certifications

- The Act requires that an ANDA contain a certification for each patent listed in the Orange Book for the innovator drug. This certification must state one of the following:
  - I. that patent information relating to the innovator drug has not been filed;
  - II. that the patent has expired;
  - III. that the patent will expire on a particular date; or
  - IV. that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which approval is being sought.

Patent Certifications

- A certification under paragraph I or II permits the ANDA to be approved immediately when otherwise eligible.
- A certification under paragraph III indicates that the ANDA may be approved on the patent expiration date.

- A paragraph IV certification questions whether the listed patent is valid, enforceable, or will be infringed by the proposed generic product. The ANDA applicant who files a paragraph IV certification to a listed patent must notify the patent owner and the NDA holder for the listed drug that it has filed an ANDA containing a patent challenge. If either party files a patent infringement suit against the ANDA applicant within 45 days of the receipt of notice, under most circumstances FDA may not give final approval to the ANDA for at least 30 months from the date of the notice.
- The statute provides an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification.

B-Rated Drugs

- "Orange Book"

Post Lecture Evaluation

1. The Hatch-Waxman Amendment to the FD&C Act provided a mechanism for the approval of generic drug products. True/False
2. Approval of an abbreviated new drug application requires review of large clinical studies assessing the effectiveness of the product. True/False
3. A generic drug may have a different route of administration than the reference drug. True/False
4. Facilities manufacturing generic drug products are not inspected by FDA. True/False
5. The "Orange Book" contains therapeutic equivalence evaluations. True/False
6. Drug products that are rated "A" in the "Orange Book" may be substituted with full confidence. True/False
7. To confirm bioequivalence, the rate and extent of absorption must not be statistically different when administered to humans at the same molar dose. True/False
Post Lecture Evaluation

1. There is only one way to determine bioequivalence. True/False
2. Generic NTRI drug products require different bioequivalence limits than other drug products. True/False

Resources

- OGD Website: http://www.fda.gov/cder/ogd
- Orange Book: http://www.fda.gov/cder/ob/default.htm