

Pharmacotherapy Frontiers 2007
April 21, 2007

Office of Generic Drugs



The FDA Process for Approving Generic Drugs

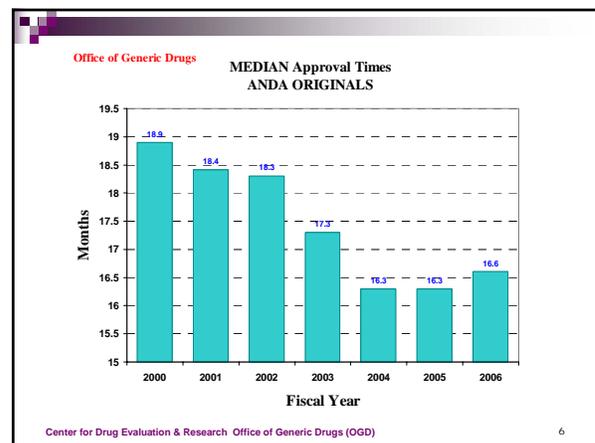
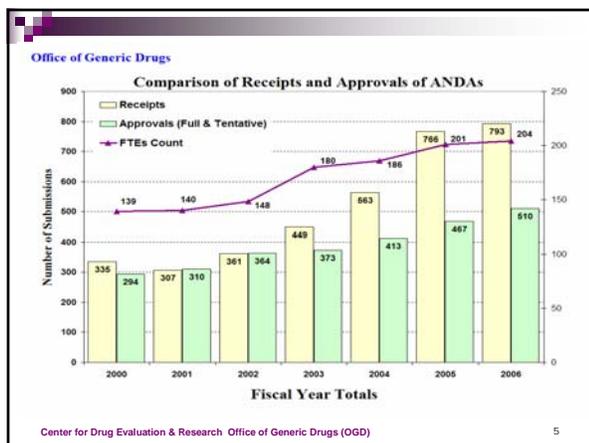
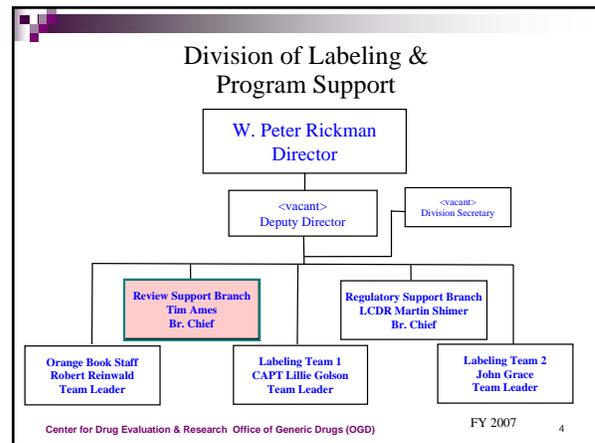
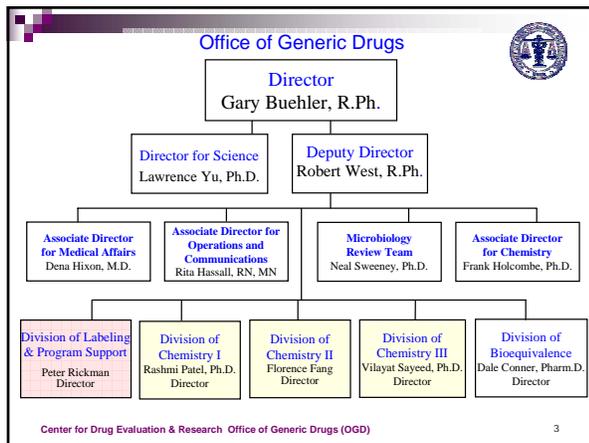
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Division of Labeling and Program Support
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The FDA Process for Approving Generic Drugs

Overview

- Office of Generic Drugs
- Perceptions about Generic Drugs
- New Drug vs. Generic Drug Approval Process
- Bioequivalence
- The 'Orange Book'

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Use other than as a learning aid for Pharmacotherapy Frontiers 2007 must be approved by the speaker

Patient Perceptions

The Negatives

Generics don't work for me

I don't trust generics

I read that generic drugs are not the real thing, they are not pure.

Why change something that is working

Generics don't seem to work as well

I have the best insurance so DAW my RX so I can have the best medications possible

I am allergic to generics

Brand name drugs taste better

Source: J.E. Billi, MD, University of Michigan Health System, October 29, 2002, "Quotes Reported by UM Physicians"

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Patient Perceptions

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?

Source: J.E. Billi, MD, University of Michigan Health System, October 29, 2002, "Quotes Reported by UM Physicians"

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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

Source: Generic Pharmaceutical Association, *Facts About Generics: Generic Pharmaceutical Facts At A Glance*, 3/25/2005. <http://www.gphaonline.org>

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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

Source: Generic Pharmaceutical Association, *Facts About Generics: Generic Pharmaceutical Facts At A Glance*, 3/25/2005. www.gphaonline.org

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THE WASHINGTON POST
TUESDAY, JANUARY 9, 2007 A8

Generic Drugs Help Slow Health-Care Spending

Health-care spending grew in 2005 at the slowest pace in six years thanks in part to a greater reliance on generic drugs.

Health spending went up 6.8 percent in 2005, approaching \$2 trillion. That represents about \$1 out of every \$5 spent in the United States, compared with about \$1 out of every \$10 in the early 1980s.

But economists aren't confident that the trend will last.

Richard S. Foster, the chief actuary for the Centers for Medicare and Medicaid Services, said there is a growing demand for expensive life-saving equipment and procedures.

Officials said generic drugs were the most important factor in slowing health-care spending in 2005. The growth in spending on medicine was lower than overall spending on health care for the first time since the early '90s.

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Drug Price Competition and Patent Term Restoration Act of 1984

- a.k.a. Hatch-Waxman Act, amends 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

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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

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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'

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What are the requirements for a generic drug application?

- Labeling
- Chemistry, Manufacturing, Controls/Microbiology
- Manufacturing Compliance
- Bioequivalence
- Legal/Regulatory

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NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	6. Bioequivalence
7. Clinical Studies	
8. Bioavailability	

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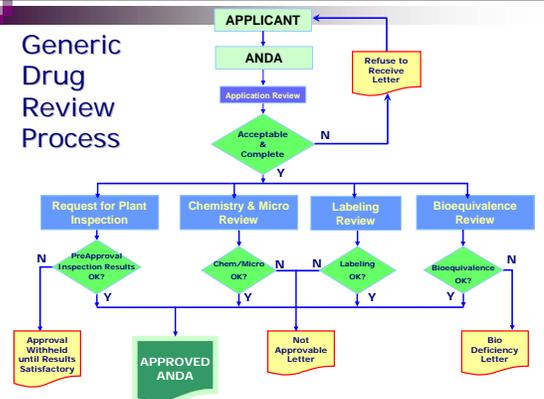
How do we assure the quality of generic drugs?

- 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

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Generic Drug Review Process



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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

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Chemistry Review

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

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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

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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

Center for Drug Evaluation & Research Working Definition

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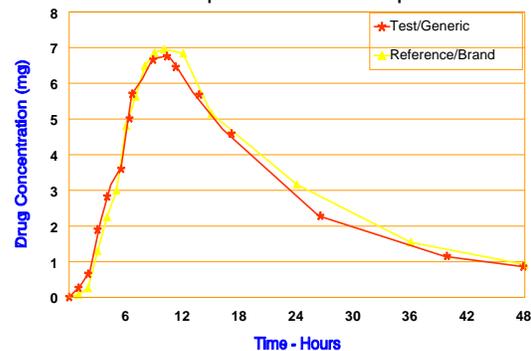
Purpose of BE Review

- 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

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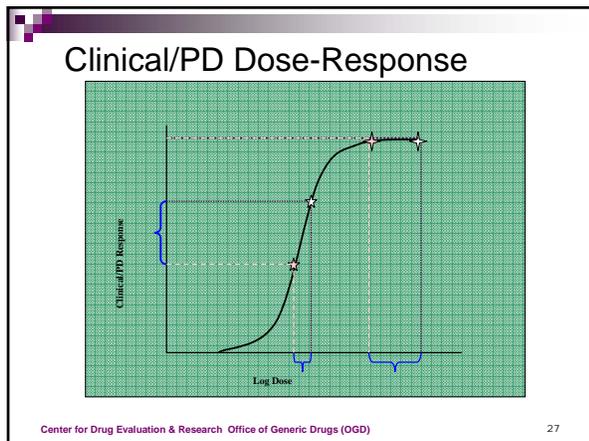
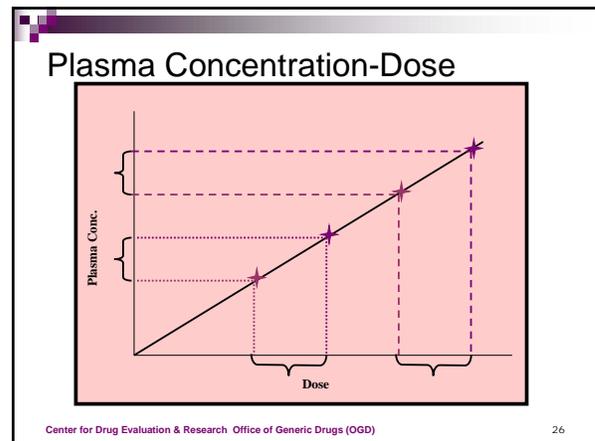
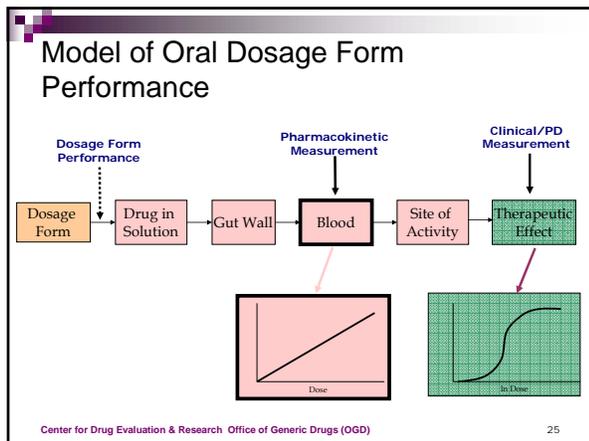
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Bioequivalence Example



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- ### Approaches to Determining Bioequivalence (21 CFR 320.24)
- In vivo measurement of active moiety or moieties in biologic fluid
 - In vivo pharmacodynamic comparison
 - Fev₂, Albuterol, Blanching Study, Topical Corticosteroid
 - In vivo limited clinical comparison
 - Topicals, Nasal Suspensions
 - In vitro comparison
 - Questtran - Binding Studies, Nasal Solutions - Sprayer Evaluation, Propofol - Droplet Size
 - Any other approach deemed appropriate by FDA
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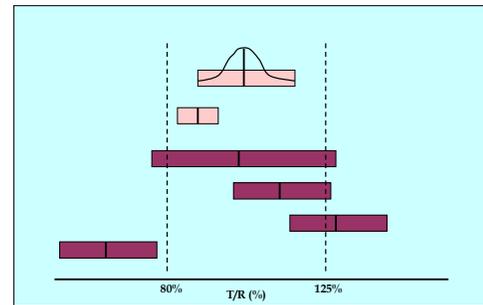
- ### Study Designs
- Single-dose, two-way crossover, fasted
 - Single-dose, two-way crossover, fed
 - Alternatives
 - Single-dose, parallel, fasted (Long Half-Life (wash-out) Amiodarone, Etidronate)
 - Single-dose, replicate design (Highly Variable Drugs)
 - Multiple-dose, two-way crossover, fasted (Less Sensitive Clozapine (Patient Trials) Chemotherapy Trials)
 - Clinical endpoint study (Topicals Nasal Suspensions)
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- ### 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
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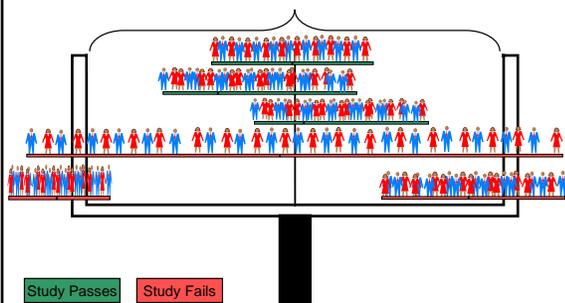
Statistical Analysis (Two One-sided Tests Procedure)

- 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)



Evaluating Bioequivalence Results



Narrow Therapeutic Index (NTI) Drugs

- Drug Products that are subject to therapeutic drug concentration or pharmacodynamic monitoring
 - Examples are: 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)

Electronic Orange Book -
<http://www.fda.gov/cder/ob/>

Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

Current through September 2006**

** In order to provide timely consumer information on generic drugs, the Electronic Orange Book will be updated daily as new generic approvals occur.
Refer to FAQ for additional information.

Annual Edition
FAQ

Search by Active Ingredient Search by Applicant Holder
Search by Proprietary Name Search by Application Number
Search by Patent

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

“Orange Book”



- 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

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B-Rated Drugs



- 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.

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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.

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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.

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Patent Certifications

- ✓ 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.

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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

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Post Lecture Evaluation

8. There is only one way to determine bioequivalence. True/False
9. Generic NTI 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>
- Online Training Seminar 'FDA Process for Approving Generic Drugs':
<http://www.connectlive.com/events/generic-drugs/>