



U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.



Generic Drugs: Overview of ANDA Review Process

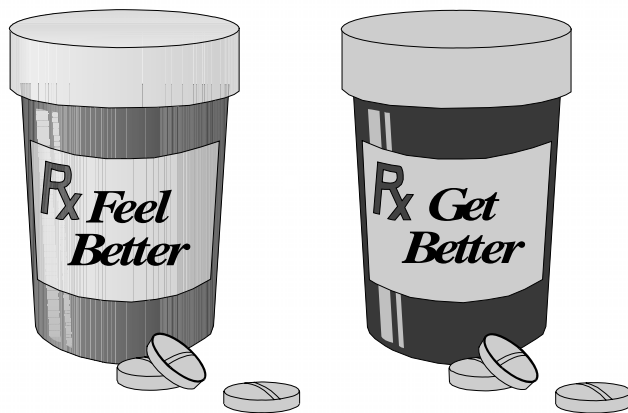
Ted Sherwood
Office of Pharmaceutical Science



CDER Forum for International Drug Regulatory Authorities



Brand vs. Generic



CDER Forum for International Drug Regulatory Authorities



What is the Main Consumer Concern Regarding Generics?

- Do the quality and performance of generic drugs compare to brand drugs?

Often triggered by brand companies and physicians



CDER Forum for International Drug Regulatory Authorities



Legislative History

- **1906 Pure Food and Drug Act** - establishes regulation of Food and Drugs
- **1938 Food, Drug and Cosmetic Act** - introduced safety standards
- **1962 Kefauver-Harris Amendments to the FDA&C Act** - tightened safety standards and introduced requirement that drugs must be effective
- **1984 Hatch-Waxman Act** - created an *abbreviated* mechanism for approval of generic copies of all drugs originally approved after 1962, by stating that pre-clinical and clinical testing did not have to be repeated for generics



CDER Forum for International Drug Regulatory Authorities



Definition of a Generic Drug

A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.



CDER Forum for International Drug Regulatory Authorities



When can a Generic Drug be Marketed?

- **After patent & exclusivity protection ends, or**
- **patent owner waives its rights, and**
- **FDA requirements are met**



CDER Forum for International Drug Regulatory Authorities



Patent Protection

- 17 years from the date the patent was issued
- or*
- 20 years from the date the patent was submitted (to the Patent Office, not FDA)

Equates to approximately 12 years of marketing protection.



CDER Forum for International Drug Regulatory Authorities



Patent Filing

- Granted by U.S. Patent and Trademark Office
 - Submitted to/for NDAs only
 - Covers
 - Drug Substance – Active Ingredient
 - Method of Use – Indication
 - Drug Product – Formulation, Composition
 - Published in Orange Book
 - Delays final approval date of ANDAs
- Approximately 240 patents listed in Orange Book will expire in the next 5 years***



CDER Forum for International Drug Regulatory Authorities



Patent Certification

- I Patent Not Submitted to FDA - approval effective after OGD scientific determination
- II Patent Expired - approval effective after OGD scientific determination
- III Patent Expiration Date (honored) – tentative approval after OGD scientific determination, final approval when patent expires
- IV Patent Challenge – tentative approval after OGD science determination, final approval when challenge won



CDER Forum for International Drug Regulatory Authorities



Patent Challenge Process

- Paragraph IV certification by ANDA holder declaring patent invalid, not infringed, or not enforceable
- Notification provision on ANDA holder
- 45-Day clock
 - No lawsuit – challenge successful
 - Lawsuit – 30 months (risk of marketing after meeting FDA approval criteria) or final court decision, whichever earlier



CDER Forum for International Drug Regulatory Authorities



Patent Challenge Successful – Award of 180-Day Exclusivity Period

- Awarded to first ANDA holder to file a complete application with patent challenge
- Protection from other generic competition – blocks approval of subsequent ANDAs
- Protection triggered by:
 - First commercial marketing
 - Forfeiture provisions



CDER Forum for International Drug Regulatory Authorities



Exclusivity

*FDA controlled reward primarily to
brand name/new drug companies
for continued development*



CDER Forum for International Drug Regulatory Authorities



Orphan Drug Exclusivity (ODE)

- Orphan drug refers to a product that treats a rare disease - affecting fewer than 200,000 Americans
- 7 years exclusivity
- Granted on approval of designated orphan drug
- OGD works with the Office of Orphan Products



CDER Forum for International Drug Regulatory Authorities



New Chemical Entity (NCE)

- 5 years exclusivity
- Applies to NCEs approved after September 24, 1984



CDER Forum for International Drug Regulatory Authorities



“Other”/Waxman-Hatch

- 3 years exclusivity
- Applies to “significant” approved change where new clinical studies (other than bioavailability studies) were conducted by the NDA holder and were essential for FDA’s approval.
- Changes include new: dosage form, strength, route of administration, indication, dosing regimen, Rx to OTC switch



CDER Forum for International Drug Regulatory Authorities



Pediatric

- 6 months of exclusivity
- Additive to patent or other exclusivity protection
- Applies to all applications held by the NDA holder for that active moiety



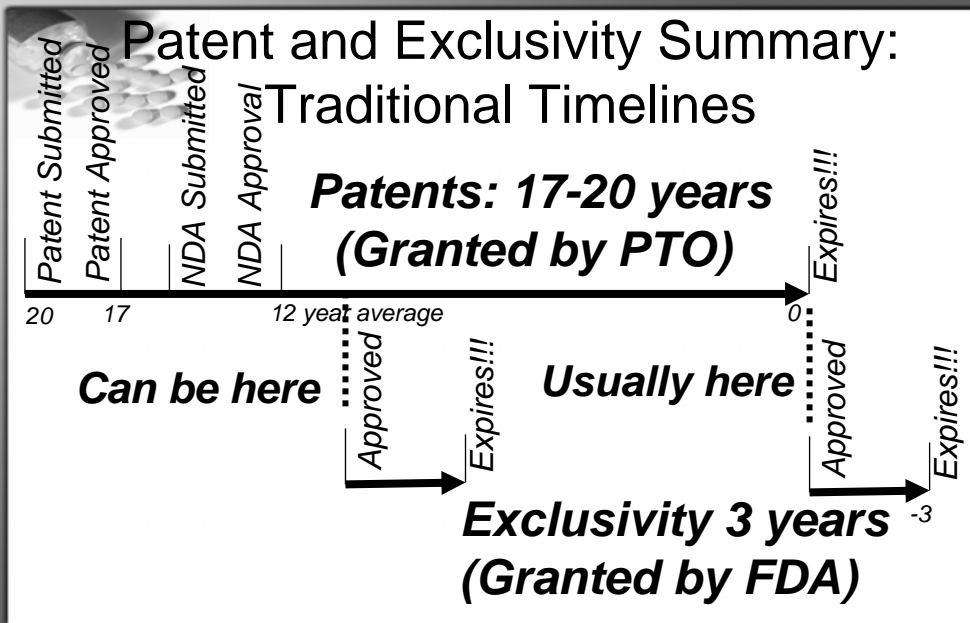
CDER Forum for International Drug Regulatory Authorities



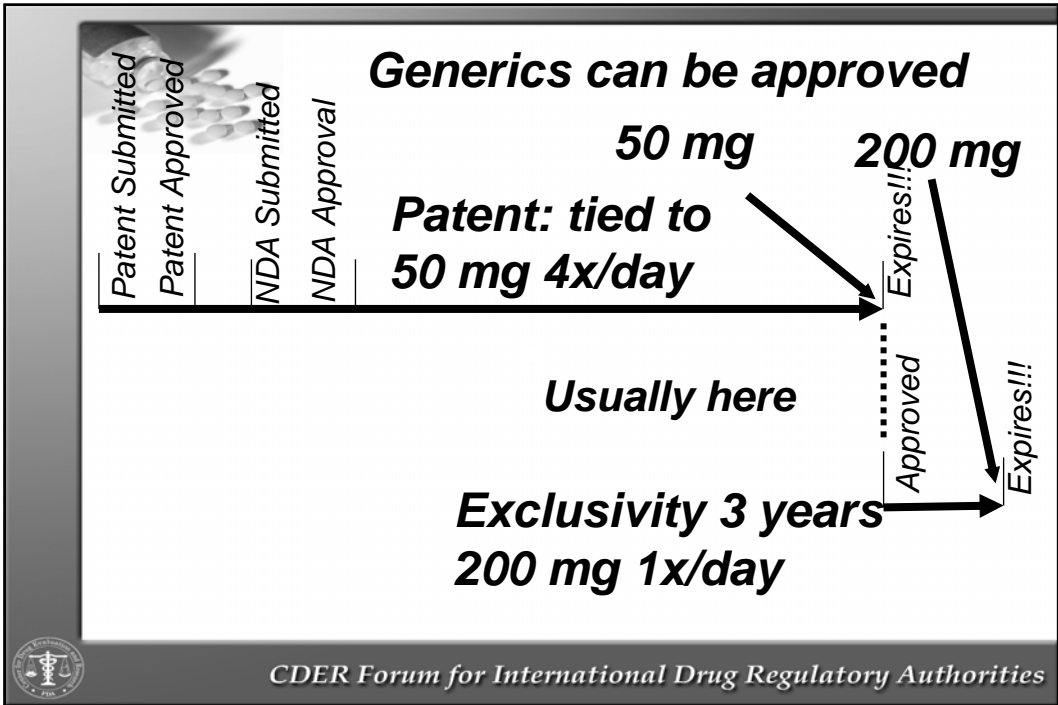
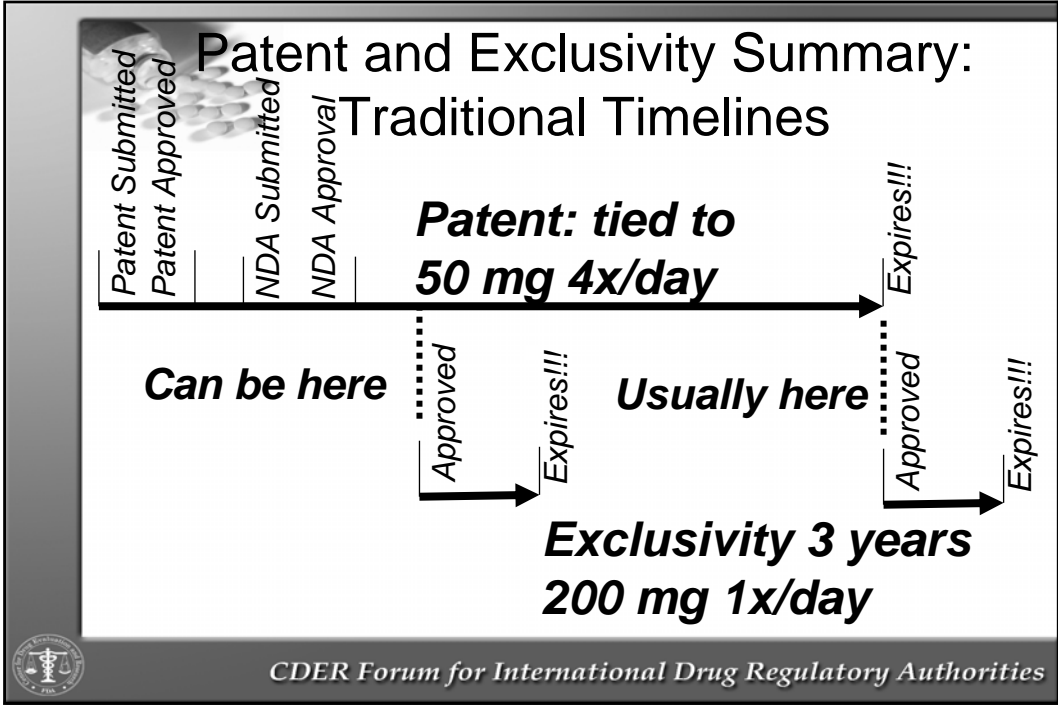
Patent and Exclusivity Questions

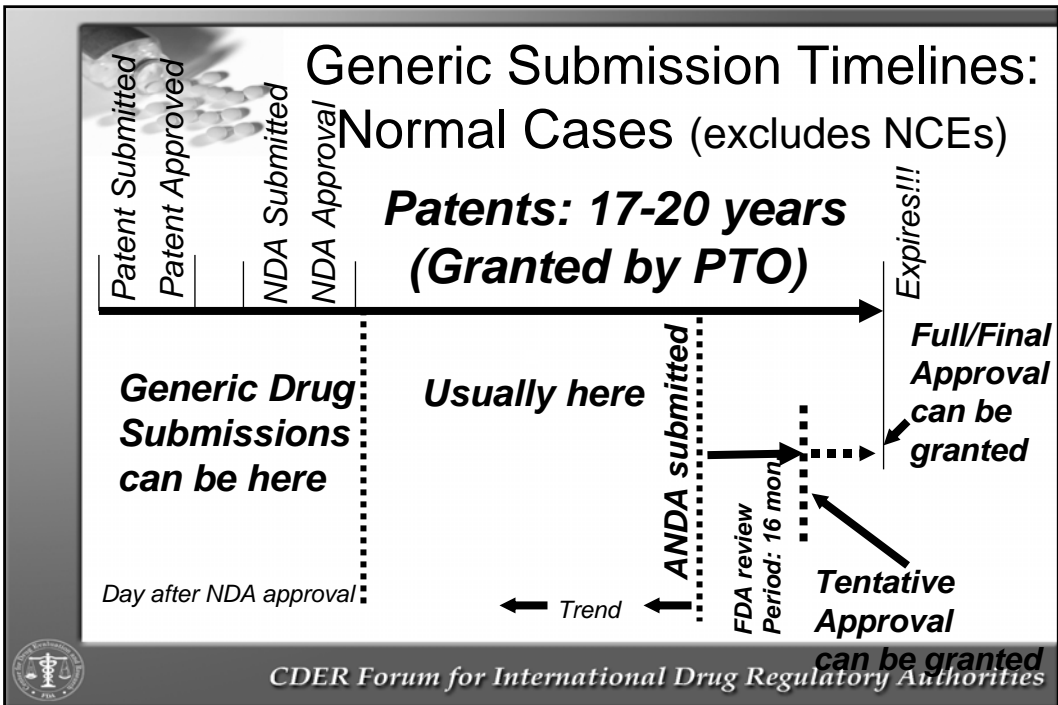
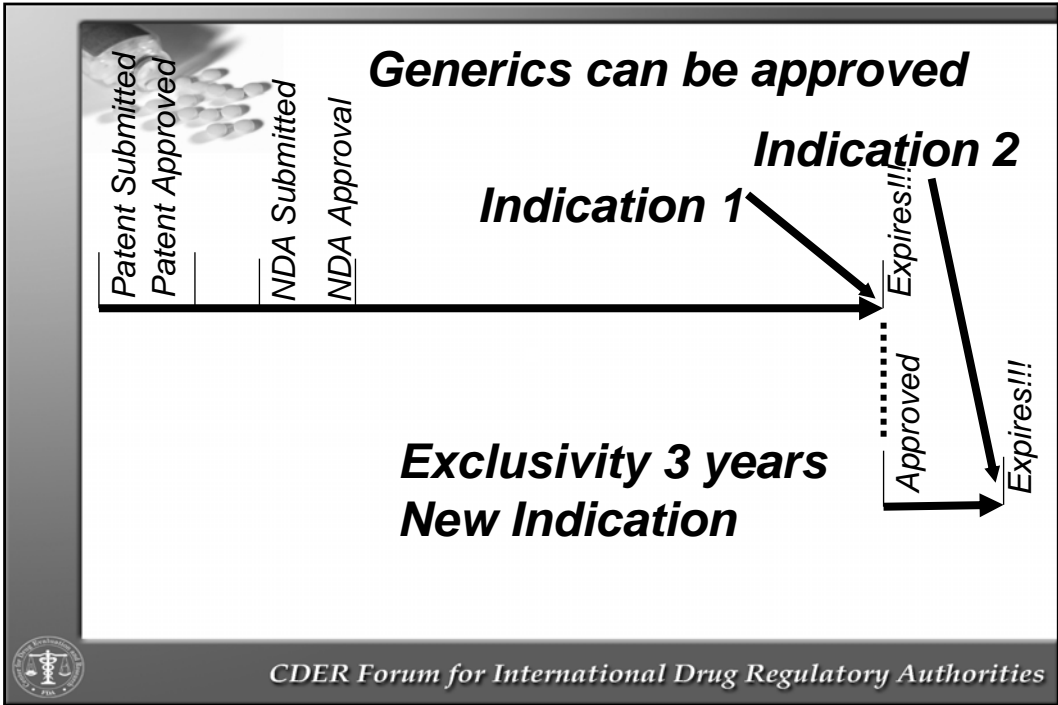


CDER Forum for International Drug Regulatory Authorities



CDER Forum for International Drug Regulatory Authorities







What are the Basic Generic Drug Requirements?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Inactive ingredients already approved in a similar NDA



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

<u>(NDA) Requirements</u>	<u>(ANDA) Requirements</u>
---------------------------	----------------------------

- | | |
|----------------------|--------------------|
| 1. Labeling | 1. <u>Labeling</u> |
| 2. Pharm/Tox | 2. Pharm/Tox |
| 3. Chemistry | 3. Chemistry |
| 4. Manufacturing | 4. Manufacturing |
| 5. Controls | 5. Controls |
| 6. Microbiology | 6. Microbiology |
| 7. Inspection | 7. Inspection |
| 8. Testing | 8. Testing |
| 9. Animal Studies | 9. Bioequivalence |
| 10. Clinical Studies | |
| 11. Bioavailability | |



CDER Forum for International Drug Regulatory Authorities



Labeling

- “Same” as brand name labeling
- May delete portions of labeling protected by patent or exclusivity (i.e., an indication)
- May differ in excipients and product description (i.e., colors, shapes)



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

(NDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



CDER Forum for International Drug Regulatory Authorities



Pharm/Tox

- All inactive ingredients must be approved in either the reference listed drug or similar NDA in same or higher levels. (FDA publishes the ingredient and highest approved levels.)
- Generic focus – is there anything unique to using this ingredient in the proposed generic



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

(NDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



CDER Forum for International Drug Regulatory Authorities



Chemistry, Manufacturing and Controls (CMC)

- Components and composition
- Manufacturing and Controls
- Batch formulation and records
- Description of facilities
- Specifications and testing
- Packaging
- Stability



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

(NDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



CDER Forum for International Drug Regulatory Authorities



Microbiology

- Assure the sterility of the product through the manufacturing process – especially important with injectable drug products



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

(NDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



CDER Forum for International Drug Regulatory Authorities



Inspections/Testing

- Assure adherence to and authenticity of data submitted in the application
- Assure manufacturing facilities are in compliance with current good manufacturing practices (CGMPs)
- Assure bioequivalence sites are in compliance with current good clinical practices (CGCPs)
- Conducted primarily by Field/Office of Regulatory Affairs with support from Center (Office of Compliance) and assigned geographically



CDER Forum for International Drug Regulatory Authorities



NDA vs. ANDA Review Process

(NDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

(ANDA) Requirements

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence



CDER Forum for International Drug Regulatory Authorities



What is Bioequivalence?

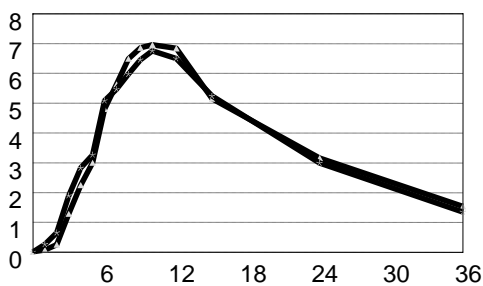
A generic drug is considered to be bioequivalent to the brand name drug if:

- The rate and extent of absorption do *not* show a significant difference from listed drug, or
- The extent of absorption does *not* show a significant difference and any difference in rate is intentional or not medically significant

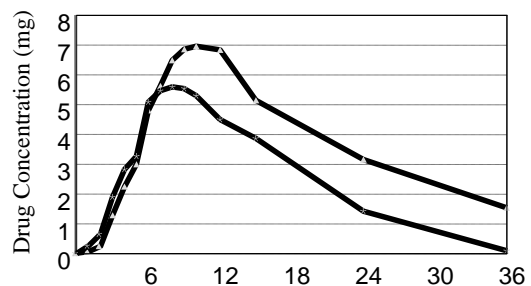


CDER Forum for International Drug Regulatory Authorities

Bioequivalent



Inequivalent

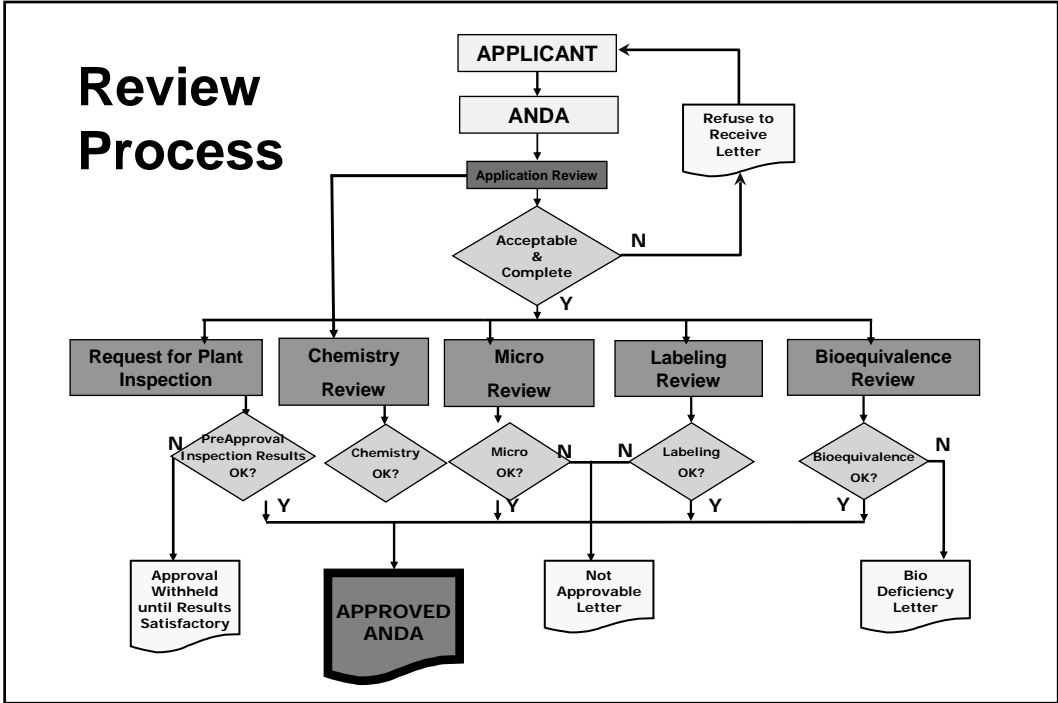



Time Hours

— Test/Generic


- - Reference/Brand

Time Hours

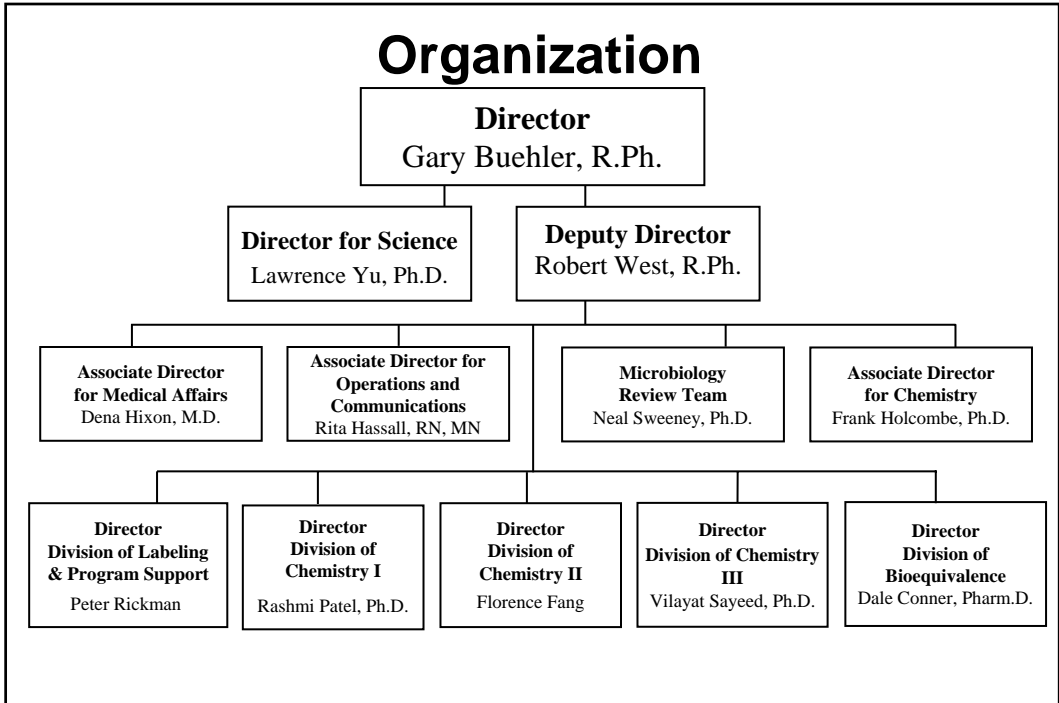




OGD Staff

<u>Total</u>	<u>240</u>
Chemist	105
Bioequivalence/ Pharmacologists	35
Project Managers/ Pharmacists	65
Microbiologists	11
Medical Officers	2
Math Statisticians	2
IT Specialists	3
Admin/Support Staff	17




CDER Forum for International Drug Regulatory Authorities





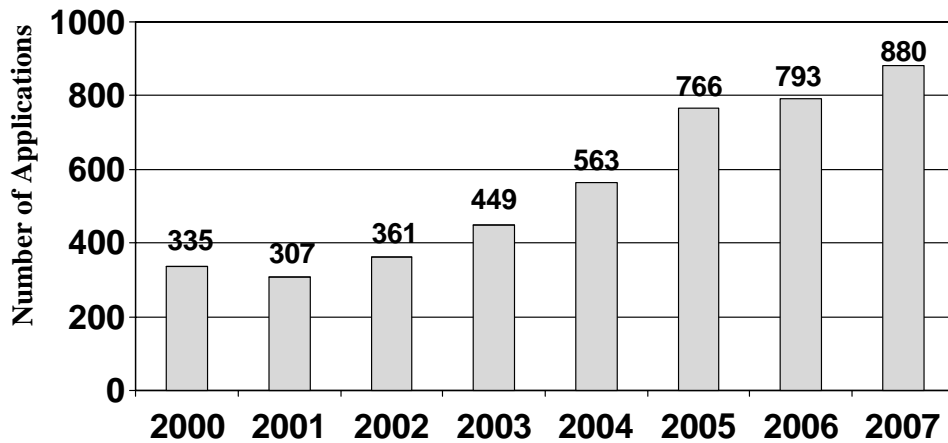
Generic Drug Review Process Issues

- **Consistency between reviews of multiple applications for the same drug**
- **Fairness in timing of reviews**
- **Patent/exclusivity issues**
- **Demonstration of Bioequivalence**



CDER Forum for International Drug Regulatory Authorities

Receipts



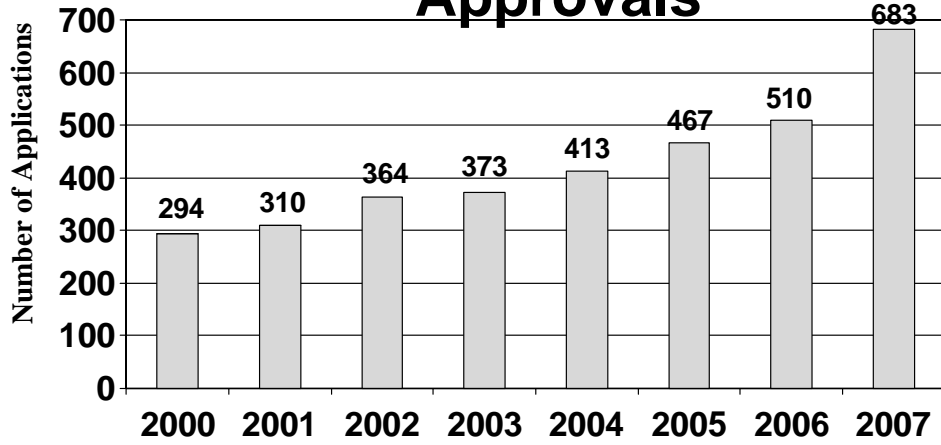
Communications with ANDA Holders

- Acknowledgement of Receipt Letter
 - States date of application filing
- Refuse to Receive (82/year)
- Deficiency Actions (Bio and Labeling)
- Not Approvable Actions (CMC) (944/year)
 - Minor deficiencies – 60-day review clock
 - Major deficiencies – 180-day review clock
- Tentative Approval – approval pending patent expiration/resolution
- Approval – drug product can be marketed

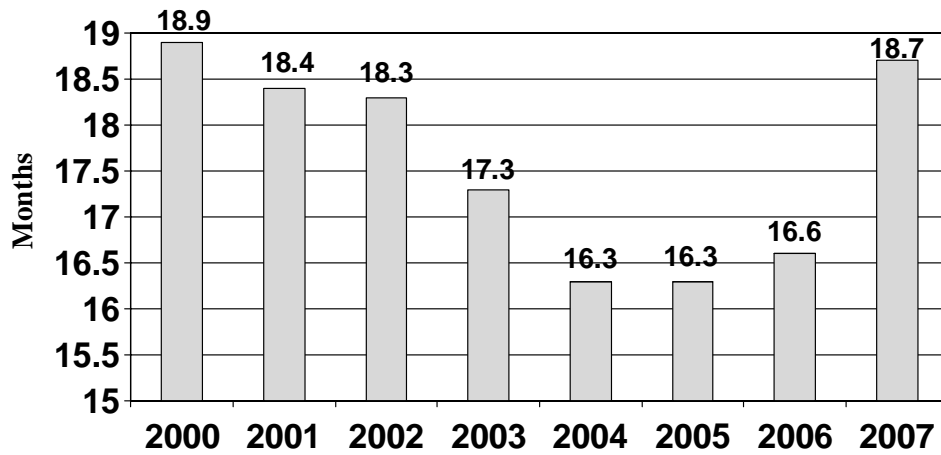


CDER Forum for International Drug Regulatory Authorities

Approvals & Tentative Approvals



Approvals Times (Median)





Post Marketing

- Changes to an approved ANDA (21 CFR 314.70)
 - Supplements (3500 received/year)
 - ↳ Changes Being Effective (CBE)
 - ↳ Changes Being Effective in 30-days (CBE-30)
 - ↳ Prior Approval Supplement (PAS)
 - Annual Report (6000 received/year)
 - ↳ Summary of product
 - ↳ (current) Labeling
 - ↳ Distribution data



CDER Forum for International Drug Regulatory Authorities



Post Marketing (cont.)

- Reporting of Adverse Drug Events
(21 CFR 314.80 and 314.98)
 - 15-Day “Alert Reports” (both serious and unexpected)
 - Periodic Adverse Drug Experience Reports - quarterly for the first three years post-approval and annually thereafter



CDER Forum for International Drug Regulatory Authorities



Post Marketing (cont.)

- Manufacturing Compliance Programs
 - Purpose to assure quality of marketed drug products
 - Mechanisms
 - ✦ Surveillance
 - ✦ Manufacturing/testing plant inspections to assess ANDA holder's continued compliance with good manufacturing practices



CDER Forum for International Drug Regulatory Authorities



Post Marketing (cont.)

- Therapeutic Inequivalence Action Coordinating Committee
 - Evaluates reports and related information on possible therapeutic failures and toxicity that are attributed to inequivalence for drug products
 - Recommendations regarding appropriate regulatory actions to be taken based on a scientific evaluation and risk assessment



CDER Forum for International Drug Regulatory Authorities



Post Marketing (cont.)

- Promotional Materials – for all brand and generic drug prescription products
- Product quality surveys – a recent review of 1,159 studies submitted to OGD revealed that the average difference between generics and their respective brand drugs was 3%



CDER Forum for International Drug Regulatory Authorities



How is Generic Drug Quality Assured?

- First 8 steps of review process identical to NDA process
- Bioequivalence requirements for ANDA's same as NDA's
- FDA has experience with the product
- Product is known to be safe
- Scientific literature published
- Over half are produced by brand name manufactures
- Post-approval product surveys



CDER Forum for International Drug Regulatory Authorities

To make sure your
generic drug
meets your approval,
it first has to get ours.

When FDA approves your generic drugs, it ensures they are 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.



Special Initiatives



CDER Forum for International Drug Regulatory Authorities



Critical Path Initiative

- Medical product development path is becoming increasingly challenging, inefficient and costly
- Need to update tools used to assess safety and efficacy
- “Toolkit” should contain powerful new scientific and technical methods to improve predictability and efficiency along the critical path from laboratory concept to commercial product



CDER Forum for International Drug Regulatory Authorities



Question Based Review

- Keep review up to date with advances in manufacturing and formulation science
 - Quality by Design
 - Process Analytical Technology
- Specifications based on benefit to the consumer – eliminate non-scientific controls with no value to product quality
- Product specific risk assessment
 - Reduce supplements
 - Use FDA resources effectively



CDER Forum for International Drug Regulatory Authorities



Quality by Design

- Understanding the product as it is developed and designed
- Understanding critical attributes
- Designing product and process to be robust with regard to these attributes
- Knowing what happens to those attributes if changes are made in production
- Provide the tools to utilize risk based approaches



CDER Forum for International Drug Regulatory Authorities



Process Analytical Technology

- A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.



CDER Forum for International Drug Regulatory Authorities



International Conference on Harmonization (ICH)

- To harmonize the interpretation and application of technical guidelines and requirements
- To reduce or eliminate duplicate testing during research and development in participating countries



CDER Forum for International Drug Regulatory Authorities



President's Emergency Plan for Acquired Immunodeficiency Syndrome Relief (PEPFAR)

- Standard but expedited ANDA review
- Several ANDAs approved



CDER Forum for International Drug Regulatory Authorities

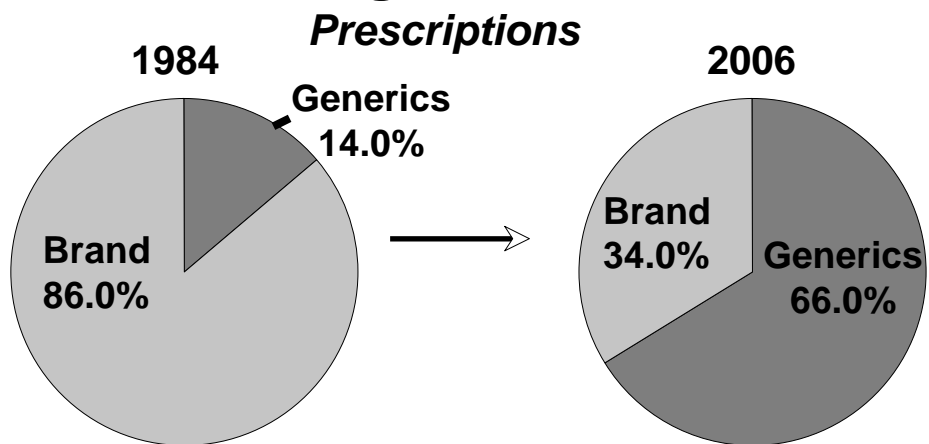


Economics



CDER Forum for International Drug Regulatory Authorities

How Frequently are Generic Drugs Used?



GPhA

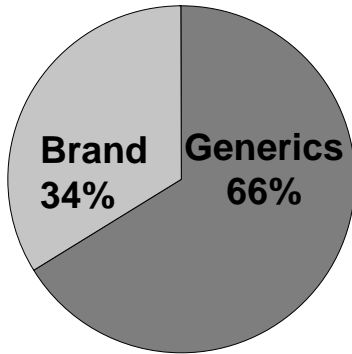
Market Share vs. Dollar

*Prescription
Volume*

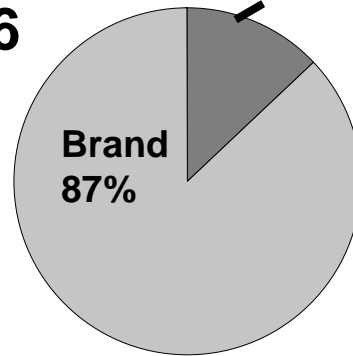
Volume?

Sales

**Generics
13.0%**



2006



GPhA May 2003 and CNN/Money Aug. 2005



Estimated Savings Through Generic Drug Use

\$67 per retail prescription

or

\$10.0 Billion a Year

(just in the U.S.)

DHHS Dec. 2004 "if consumers were to buy generic products whenever possible ... we estimate savings to be approximately \$17 billion."

GPhA May 2005

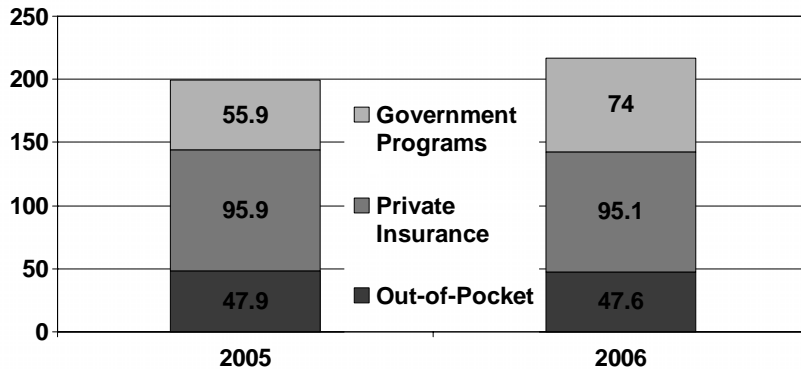


CDER Forum for International Drug Regulatory Authorities



Drug Spending

Retail Rx Drugs In Billions



CMS



CDER Forum for International Drug Regulatory Authorities



Typical Price Comparisons

Drug	Generic Price \$/30	Brand Price \$/30
Lisinopril (Zestril®) 20 mg	20.69	46.69
Citalopram (Celexa®) 20 mg	52.99	100.99
Ciprofloxacin (Cipro®) 500 mg	88.59	215.99
Metformin (Glucophage®) 1000 mg	30.69	71.59
Fluconazole (Diflucan®) 200 mg	372.99	609.99
Fluoxetine (Prozac®) 20 mg	32.29	139.99

Source: Washington metropolitan area pharmacies, March 2005.



CDER Forum for International Drug Regulatory Authorities



Future

- Over a \$50 billion worth of drug products losing protection in the next five years

August 3, 2005: 5:52 PM EDT
By Aaron Smith, CNN/Money staff writer



CDER Forum for International Drug Regulatory Authorities



Value of Generics

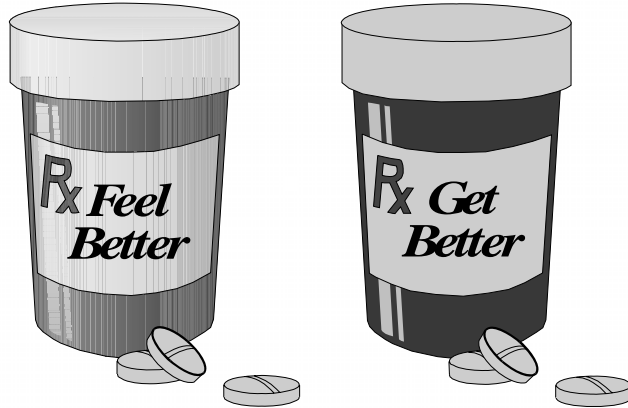
- Reduce Drug Costs
- Increase Drug Use
- Prevent Drug Shortages
 - Product rationalization
 - Supply disruption



CDER Forum for International Drug Regulatory Authorities



Brand vs. Generic



CDER Forum for International Drug Regulatory Authorities



Summary



CDER Forum for International Drug Regulatory Authorities



APPROVED DRUG PRODUCTS

WITH
THERAPEUTIC EQUIVALENCE EVALUATIONS

27TH EDITION


THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER
SECTIONS 505 AND 507 OF THE FEDERAL FOOD, DRUG, AND
COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MANAGEMENT
DIVISION OF DATABASE MANAGEMENT

2007




CDER Forum for International Drug Regulatory Authorities



"Orange Book"

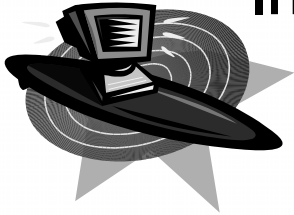
- All FDA approved drug products listed (NDA's, ANDA's and non-monograph OTC's)
- Therapeutic equivalence codes: NDAs & ANDAs
 - "A" = Substitutable
 - "B" = Inequivalent, NOT substitutable
- Expiration dates: patent and exclusivity
- Reference Listed Drugs - brand drugs identified by FDA for generic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



CDER Forum for International Drug Regulatory Authorities



Orange Book Internet Address



<http://www.fda.gov/cder/orange/default.htm>



CDER Forum for International Drug Regulatory Authorities



Other Generic Drug Links

- Office of Generic Drugs Home Page:

<http://www.fda.gov/cder/ogd/index.htm>

- On line training program:

<http://www.fda.gov/cder/learn/CDERLearn/genDrugProcess/transcript.htm>



CDER Forum for International Drug Regulatory Authorities



Questions:

Ted Sherwood

Special Assistant to the Director
Office of Pharmaceutical Science, CDER

White Oak, Bldg 21, Room 3528

10903 New Hampshire Ave.

Silver Spring, MD 20903-0002

Tel: 301-796-1605, Fax: 301-796-9733

edward.sherwood@fda.hhs.gov



CDER Forum for International Drug Regulatory Authorities