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Generic Drugs: Overview of ANDA Review Process

Ted Sherwood
Office of Pharmaceutical Science

Brand vs. Generic

Rx Feel Better	xn
Rx Get Better
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

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
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.

When can a Generic Drug be Marketed?

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

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
**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

**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
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

Exclusivity

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

New Chemical Entity (NCE)

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

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
Patent and Exclusivity Questions

Patent and Exclusivity Summary:

Traditional Timelines

- Patents: 17-20 years (Granted by PTO)
- Exclusivity 3 years (Granted by FDA)

Timeline:
- Patent Submitted
- Patent Approved
- NDA Submitted
- NDA Approval
- Expiration

Can be here
- Usually here

Approved
Expires!!!

20 17 12 year average 0

CDER Forum for International Drug Regulatory Authorities
Patent and Exclusivity Summary:

Traditional Timelines

<table>
<thead>
<tr>
<th>Patent Submitted</th>
<th>Patent Approved</th>
<th>NDA Submitted</th>
<th>NDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent: tied to</td>
<td>50 mg 4x/day</td>
<td>Approved</td>
<td>Expires!!!</td>
</tr>
<tr>
<td>200 mg 1x/day</td>
<td></td>
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Can be here

Usually here

Exclusivity 3 years

200 mg 1x/day

Generics can be approved

50 mg

200 mg

Patent: tied to

50 mg 4x/day

Usually here

Exclusivity 3 years

200 mg 1x/day

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Generics can be approved

**Indication 2**

**Exclusivity 3 years**

**New Indication**

**Indication 1**

Expires!!!

**Patent Submitted**

NDA Submitted

NDA Approval

Patent Approved

NDA Submitted

NDA Approval

Patent Submitted

**Generic Submission Timelines:**

**Normal Cases (excludes NCEs)**

**Patents: 17-20 years**

(Granted by PTO)

**Generic Drug Submissions can be here**

**Usually here**

ANDA submitted... Full/Final Approval can be granted

FDA review Period: 16 mon...

Tentative Approval can be granted

Day after NDA approval

Trend
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

NDA vs. ANDA Review Process

(NDA) Requirements (ANDA) Requirements
1. Labeling 1. Labeling
2. Pharm/Tox 2. Pharm/Tox
3. Chemistry 3. Chemistry
5. Controls 5. Controls
7. Inspection 7. Inspection
8. Testing 8. Testing
9. Animal Studies
10. Clinical Studies
### 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)

### NDA vs. ANDA Review Process

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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

NDA vs. ANDA Review Process

(NDA) Requirements  (ANDA) Requirements
1. Labeling 1. Labeling
2. Pharm/Tox 2. Pharm/Tox
3. Chemistry 3. **Chemistry**
4. Manufacturing 4. **Manufacturing**
5. Controls 5. **Controls**
7. Inspection 7. Inspection
8. Testing 8. Testing
10. Clinical Studies
11. Bioavailability
NDA vs. ANDA Review Process

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2. Pharm/Tox  2. Pharm/Tox
3. Chemistry  3. Chemistry
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7. Inspection  7. Inspection
8. Testing  8. Testing
10. Clinical Studies
11. Bioavailability
**Microbiology**

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

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**NDA vs. ANDA Review Process**

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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

NDA vs. ANDA Review Process

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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.

<table>
<thead>
<tr>
<th>Bioequivalent</th>
<th>Inequivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Hours</td>
<td>Test/Generic</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Drug Concentration (mg)</td>
<td>0</td>
</tr>
</tbody>
</table>

CDER Forum for International Drug Regulatory Authorities
Review Process

APPLICANT

ANDA

Application Review

Acceptable & Complete

Y

N

Approval Withheld until Results Satisfactory

APPROVED ANDA

PreApproval Inspection Results OK?

Y

N

Not Approvable Letter

Bioequivalence OK?

N

Bio Deficiency Letter

Y

Labeling OK?

N

Not Approvable Letter

Micro OK?

N

Chemistry OK?

Y

Chemistry Review

Micro Review

Labeling Review

Bioequivalence Review

Request for Plant Inspection

OGD Staff

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

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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
Receipts

Number of Applications

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
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<tbody>
<tr>
<td>2000</td>
<td>335</td>
</tr>
<tr>
<td>2001</td>
<td>307</td>
</tr>
<tr>
<td>2002</td>
<td>361</td>
</tr>
<tr>
<td>2003</td>
<td>449</td>
</tr>
<tr>
<td>2004</td>
<td>563</td>
</tr>
<tr>
<td>2005</td>
<td>766</td>
</tr>
<tr>
<td>2006</td>
<td>793</td>
</tr>
<tr>
<td>2007</td>
<td>880</td>
</tr>
</tbody>
</table>

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
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

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
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

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
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%

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

When FDA approves your generic drug, 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, every drug 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 1-888INFO-FDA to learn more.

Generic Drugs: Safe. Effective. FDA Approved.

Special Initiatives
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

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
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

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.
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

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

- Standard but expedited ANDA review
- Several ANDAs approved
How Frequently are Generic Drugs Used?

Prescriptions

1984
- Generics: 14.0%
- Brand: 86.0%

2006
- Brand: 34.0%
- Generics: 66.0%

GPhA
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
Typical Price Comparisons

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

Future

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

Value of Generics

- Reduce Drug Costs
- Increase Drug Use
- Prevent Drug Shortages
  - Product rationalization
  - Supply disruption
Brand vs. Generic

Rx Feel Better

Rx Get Better

Summary
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

“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
Orange Book
Internet Address

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

Other Generic Drug Links

- Office of Generic Drugs Home Page:
  http://www.fda.gov/cder/ogd/index.htm

- Online training program:
Questions:

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