Outline

- Compare and contrast between the generic drugs and new drugs
- Generic drug application filing and regulatory review
- Achievements and challenges in the regulatory review for generic drug applications
- Career opportunities in generic drug regulatory review
New Drug Application (NDA)

- NDA is submitted based on FD&C Act 505(b).

- NDAs are submitted for:
  - New molecular entity
  - New formulation of previously approved drug
  - New combination of two or more drugs
  - New indication (claim) for already marketed drug
Abbreviated New Drug Application (ANDA)

- ANDA is submitted based on FD&C Act 505(j).

- ANDAs are submitted for:
  - Generic drugs; a NDA must be previously approved and listed, known as the reference listed drug (RLD)

Note: ANDA may not be submitted for five years after the date of the approval of the New Molecular Entity (NME).
# Requirements for NDA vs. ANDA

## NDA
1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspections
6. Animal Studies
7. Clinical Studies
8. Bioavailability

## ANDA
1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspections
6. Bioequivalence
Submission for NDA vs. ANDA

<table>
<thead>
<tr>
<th>Module 1</th>
<th>Module 2</th>
<th>Module 3</th>
<th>Module 4</th>
<th>Module 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional Administrative</td>
<td>Summaries</td>
<td>Quality</td>
<td>Nonclinical Study Reports</td>
<td>Clinical Study Reports</td>
</tr>
<tr>
<td>Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.14 Labeling</td>
<td>2.3 Quality Overall Summary (QOS)</td>
<td>Chemistry, Manufacturing, Controls,</td>
<td></td>
<td>5.3.1 Bioequivalence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and Testing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICH M4: Common Technical Document for the Registration
CTD Submission Format Example

Based on the ICH M4Q: The CTD – Quality, the follow drug substance information should be included:

- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
Patent and Exclusivity

- **Patents** are granted by the *Patent and Trademark Office* anywhere along the development lifeline of a drug and can encompass a wide range of claims.
  - Patents expire 20 years from the date of filing. Many other factors can affect the duration of a patent.

- **Exclusivity** is exclusive marketing rights granted by the *FDA* upon approval of a drug and can run concurrently with a patent or not.
  - Orphan Drug (ODE) - 7 years
  - New Chemical (NCE) - 5 years
  - Pediatric Exclusivity (PED) - 6 months added
  - "Other" Exclusivity - 3 years for a "change" if criteria are met
  - Patent Challenge (PC) - 180 days (*this exclusivity is for ANDAs only*)
# Patent for NDA vs. ANDA

<table>
<thead>
<tr>
<th>NDA</th>
<th>ANDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patent information is required to be submitted with all new drug applications at the time of submission of the NDA.</td>
<td>- A certification for each patent listed in the “Orange Book” for the RLD must state one of the following:</td>
</tr>
<tr>
<td>- FDA relies on the NDA applicant or patent owner’s signed declaration stating that the patent covers an approved drug product’s formulation, composition or use.</td>
<td>(I) No Patent Filed</td>
</tr>
<tr>
<td></td>
<td>(II) Patent Has Expired</td>
</tr>
<tr>
<td></td>
<td>(III) Patent Will Expire</td>
</tr>
<tr>
<td></td>
<td>(IV) Patent Challenge</td>
</tr>
</tbody>
</table>
Review Process for NDA vs. ANDA

<table>
<thead>
<tr>
<th>NDA</th>
<th>ANDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower volume (average 25 approvals/year)</td>
<td>Higher volume (more than 500 approvals/year)</td>
</tr>
<tr>
<td>Higher complexity (pre-clinical and/or clinical trials, etc.)</td>
<td>Lower complexity (safety and efficacy already established)</td>
</tr>
<tr>
<td>One drug one application</td>
<td>One drug multiple applications</td>
</tr>
<tr>
<td>Pre-submission face-to-face meetings (IND phases)</td>
<td></td>
</tr>
<tr>
<td>User fee (PDUFA) from 1992</td>
<td>User fee (GDUFA) from 2013</td>
</tr>
</tbody>
</table>
## User Fee Rates for NDA vs. ANDA

<table>
<thead>
<tr>
<th></th>
<th>FY 2013</th>
<th>FY 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NDA (PDUFA)</td>
<td>ANDA (GDUFA)</td>
</tr>
<tr>
<td>Total Fee for FY</td>
<td>$718,669,000</td>
<td>$299,000,000</td>
</tr>
<tr>
<td>New Application</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(with clinical data)</td>
<td>$1,958,800</td>
<td>$2,169,100</td>
</tr>
<tr>
<td></td>
<td>$51,520</td>
<td>$63,860</td>
</tr>
<tr>
<td>(without clinical data)</td>
<td>$979,400</td>
<td>$1,084,550</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PAS only)</td>
<td>$25,760</td>
<td>$31,930</td>
</tr>
<tr>
<td>(with clinical data)</td>
<td>$979,400</td>
<td>$1,084,550</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II DMF</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>$21,340</td>
<td>$31,460</td>
</tr>
<tr>
<td>Facility</td>
<td>$526,500</td>
<td>$554,600</td>
</tr>
<tr>
<td>(Domestic/ Foreign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(FDF)</td>
<td>$175,389 / $190,389</td>
<td>$220,152 / $235,152</td>
</tr>
<tr>
<td>(API)</td>
<td>$26,485 / $41,458</td>
<td>$34,515 / $49,515</td>
</tr>
<tr>
<td>Product</td>
<td>$98,380</td>
<td>$104,060</td>
</tr>
<tr>
<td>Backlog</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Note: The rates are based on Federal Register Vol.77 No.207 (10/25/2012) and Vol.78 No.149 (8/2/2013).
Outline

- Compare and contrast between the generic drugs and new drugs
- Generic drug application filing and regulatory review
- Achievements and challenges in the regulatory review for generic drug applications
- Career opportunities in generic drug regulatory review
Requirement for ANDAs

- Must have an approved reference product (RLD) and a patent certification
- Must be *Therapeutic Equivalent* to a reference product
- Meet the quality standards for chemistry and/or microbiology
- All related facilities have acceptable cGMP compliance
Therapeutic Equivalence

Therapeutic Equivalence includes:

- Pharmaceutically Equivalent (PE)
  - Same active ingredient(s)
  - Same dosage form
  - Same route of administration
  - Identical in strength or concentration
  - May differ in characteristics such as shape, excipients, packaging...

- Bioequivalent (BE)
  - Two drugs demonstrate same rate and extent when they become available at the site of drug action
Generic Drug Review Process
Filing Review

- Filing review is conducted to determine whether the application is sufficiently complete to permit a substantive review.

- Acceptance/Refuse to Receive (RTR) letter is issued based on completeness of the ANDA.

- Updating the regulatory filing checklist on a quarterly basis (calendar year) and on an as needed basis.

Bioequivalence Review

- Evaluate bioequivalence study acceptability
  - Clinical portion (subject treatment)
  - Analytical portion (biological fluid analysis)
  - Statistical portion (are products bioequivalent?)

- Select appropriate in vitro dissolution method (solid dosage forms only)
  - Stability and controls testing

- Grant biowaivers where appropriate

- Review bioequivalence protocols

Bioequivalence Protocols: [http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm)
Bioequivalence

- Generic products is compared, in studies to the reference listed drug (RLD)
- Most studies compare the blood levels of the active moiety or moieties
- The generic product must be equivalent within certain pre-specified limits:

  AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80%-125%
Bioequivalence Example

Test (Generic) vs Reference (RLD)

Cmax

AUC

Drug Concentration (mg)

Time - Hours
Possible BE Results (90% CI)
Biowaivers

21 CFR Part 320 provides situations where *in vivo* bioequivalence studies can be waived:

- Solutions (parenteral, oral, *etc.*)
- Drug Efficacy Study Implementation (DESI)
- Biopharmaceutics Classification System (BCS)
- Usually lower strengths of a product line
Labeling Review

- Reviews for “Same” as brand name labeling (with exceptions)
  - Labeling text to reflect differences in excipients, specific pharmacokinetic data
  - How supplied information - packaging container
  - Pharmacy practice issues - to prevent medication errors

- May exclude portions of labeling protected by patent or exclusivity
Chemistry Review

Reviewing drug substance and drug product for:

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Product specifications
- Packaging
- Stability
Drug Substance Information

- Most generic drug product manufacturers rely on third parties for supplying drug substances.

- Drug substance suppliers submit Drug Master File (DMF) to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
Drug Master File

Type I: Facilities

**Type II: Drug Substance**

Type III: Containers & Closures (Bottles, Caps, Syringes, Stoppers, etc.)

Type IV: Colors, Flavors

Type V: Excipients or Microbiology
Type II DMF Filing/Review Process

1. Filing for Completeness Assessment and fee payment
2. Acceptable For filing
3. Checking for DMF availability
4. Purchasing and obtaining necessary information
5. Authorizing for DMF reviewing
6. Reviewing to support an ANDA

DMF Review

- DMFs are neither approved nor disapproved.

- A DMF is reviewed to determine whether it is adequate to support the particular Application that references it.
cGMP for the 21st Century

FDA’s Pharmaceutical cGMP for the 21st Century
(QbD Initiative, ICH Q8, Q9, and Q10)

Generic Applicant
Implementing QbD in development, manufacturing, and control

FDA/OGD
Developed a QbR system that assesses applicant’s QbD ANDAs
Quality by Design (QbD) - Paradigm Shift

**Past/Present Paradigm**

- ANDA Formulation/Process Submitted Without Context
- Claimed to be Acceptable Based Upon a Passing BE study to the RLD
- “Equivalence by Testing”

**QbD Paradigm**

- Systematic approach
  - QTPP/CQA: predefined target.
  - Product & process design and understanding: pharmaceutical equivalence to the RLD.
  - Control strategy: to ensure intended performance be consistently delivered.
- Asks Sponsors How They Systemically Arrived at a Bioequivalent Drug Product
- “Equivalence by Design”
Question based Review (QbR)

- Implemented for generic drugs in 2007
- QbR is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to:
  - Comprehensively assess critical formulation and manufacturing process variables
  - Set regulatory specifications relevant to quality
  - Determine the level of risk associated with the manufacture and design of the product
What are the unit operations in the drug product manufacturing process?

- Detailed flow chart
  - unit operations (blending, drying, etc),
  - equipment,
  - point of material entry,
  - identification of critical steps (with process or other controls)
- Narrative summary of the manufacturing process
- Reprocessing/reworking statement
- Executed batch record and blank product batch record
Microbiology Review

Reviewing sterile drug products (parenteral, ophthalmic, and inhalation) for:

- Product Development (container/closure integrity validation and preservative effectiveness)
- Overall sterile manufacturing process design and process controls
- Terminal sterilization/aseptic fill process validation
- Drug product specifications
- Release and stability
- Studies to support labeling
Inspection - cGMP/Compliance

- All facilities used for manufacturing, testing, packaging/storing drug substance and drug product are subject for inspections and must be in compliance at the time of approval.

- Inspection program is also design to check data integrity. If data integrity is in question all reviews will stop.

- Type of inspection includes: pre-approval, post-approval, and for cause.
ANDA Approval

All review disciplines find the ANDA acceptable and all facilities are in satisfactory standing as reviewed and inspected.

- **Full Approval** - all valid patents and exclusivities for the RLD are expired or any legal issues that may block approval of the ANDA are settled.

- **Tentative Approval** – there exist unexpired patents and exclusivities for the RLD.
“The Orange Book”

Approved Drug Products with Therapeutic Equivalence Evaluations

- Contains list of all FDA approved drug products (NDAs, ANDAs and OTCs)
- Therapeutic equivalence codes
  - “A” = Substitutable
  - “B” = NOT substitutable
- Patent and exclusivity expiration dates
- Reference Listed Drugs - A drug product identified by FDA for generic companies to compare their proposed products

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
Post-Approval Submissions

- Supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities.
  - Prior Approval Supplement (PAS) – major changes
  - Changes Being Effected (CBE) – moderate changes

- Annual report must be submitted each year within 60 days of the anniversary date of approval of the application.
  - May include some minor changes
Outline

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Economic Impact of Generic Drugs

- Generic Drugs account nearly 80 percent of the 4 billion prescriptions written in the U.S. in 2011.

- Generic Drugs cost 30% to 80% less than brand counterparts.

Source: Generic Pharmaceutical Association website (www.gphaonline.org)
Generic Drug Approvals

Fiscal Year
Number of Approvals
Tentative Approval
Full Approval
Challenges in Generic Drug Review

- Complex products and dosage forms
- Growing workload
  - Receipt of applications continue to be greater than approvals
  - Increasing complexity of review process
- GDUFA review performance commitments
ANDA Receipts

Fiscal Year

Number of Applications

2005: 766
2006: 793
2007: 880
2008: 830
2009: 859
2010: 813
2011: 893
2012: 1103
ANDA Backlog (pending review)
# GDUFA Review Performance Goals

<table>
<thead>
<tr>
<th>Category</th>
<th>FY 2013</th>
<th>FY 2014</th>
<th>FY 2015</th>
<th>FY 2016</th>
<th>FY 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original ANDA</td>
<td>Expedite review of paragraph IV and maintain pre-GDUFA productivity</td>
<td>60% in 15 months</td>
<td>75% in 15 months</td>
<td>90% in 10 months</td>
<td></td>
</tr>
<tr>
<td>Tier 1 first major amendment</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 10 months</td>
<td>75% in 10 months</td>
<td>90% in 10 months</td>
<td></td>
</tr>
<tr>
<td>Tier 1 minor amendments (1st – 3rd)</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 3 months*</td>
<td>75% in 3 months*</td>
<td>90% in 3 months*</td>
<td></td>
</tr>
<tr>
<td>Tier 1 minor amendments (4th – 5th)</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 6 months*</td>
<td>75% in 6 months*</td>
<td>90% in 6 months*</td>
<td></td>
</tr>
<tr>
<td>Tier 2 amendment</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 12 months</td>
<td>75% in 12 months</td>
<td>90% in 12 months</td>
<td></td>
</tr>
<tr>
<td>Prior approval supplements</td>
<td>Maintain pre-GDUFA productivity</td>
<td>60% in 6 months*</td>
<td>75% in 6 months*</td>
<td>90% in 6 months*</td>
<td></td>
</tr>
<tr>
<td>ANDA, amendment, and PAS in backlog on Oct 1st, 2012</td>
<td></td>
<td></td>
<td></td>
<td>Act on 90% by end of FY 2017</td>
<td></td>
</tr>
<tr>
<td>Controlled correspondences</td>
<td>Maintain pre-GDUFA productivity</td>
<td>70% in four months*</td>
<td>70% in two months*</td>
<td>90% in two months*</td>
<td></td>
</tr>
</tbody>
</table>

*10 months if inspection required
Outline

- Compare and contrast between the generic drugs and new drugs
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GDUFA Hiring

- Additional resources are needed to enable the FDA to reduce a current backlog of pending drug applications and cut the average review time required.
  - Microbiologist
  - Chemist
  - Chemical Engineer
  - Consumer Safety Officer
  - Pharmacist
  - Medical Officer
  - Operations Research Analyst
  - Interdisciplinary Scientist
  - Regulatory Counsel
Hiring Goals

- 25% in FY-13
- 50% in FY-14
- 25% in FY-15

More detailed information and coming virtual hiring event can be found online at the FDA Hiring Initiative webpage:

http://www.fda.gov/AboutFDA/WorkingatFDA/GenericDrugUserFeeHiring/default.htm
Thank You!