

The Role of Chemists in the FDA Drug Approval Process

231st ACS National Meeting
Atlanta, GA

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March 26, 2006

Presentation Outline

- Introduction
 - FDA Organization
 - CDER Organization
 - Drug Approval Process
- Role of Chemistry Reviewers within CDER
- Role of District Investigators in the Evaluation of cGMPs with ORA

FDA's Mission Statement

“.....is to protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products.”

Mission Process

1. Reviewing/Approving the drug to ensure that it is safe and effective
2. Inspecting the manufacturing facilities to ensure that the drugs are manufactured in accordance with Current Good Manufacturing Practice (cGMP) regulations.

FDA ORGANIZATION

I. The Office of the Commissioner

- Associate Commissioner for International Activities and Strategic Initiatives
- Office of the Chief Counsel (OCC)
- Office of External Relations (OER)
- Office of Legislation (OL)
- Office of Management and Systems (OMS)
- Office of Policy/Office of Planning
- Office of Regulatory Affairs (ORA)
- Office of Science and Health Coordination (OSHC)

II. Centers

CDER, CBER, CDRH, CVM, CFSAN, NCTR

Introduction – FDA Organization

- 6 Centers
- CDER: Center for Drug Evaluation and Research
 - CBER: Center for Biologics Evaluation and Research
 - CDRH: Center for Devices and Radiological Health
 - CVM: Center for Veterinary Medicine
 - CFSAN: Center for Food Safety and Applied Nutrition
 - NCTR: National Center of Toxicology Research

Introduction – CDER Organization

- Office of New Drugs (OND)
 - Effectiveness and Safety
- Office of Pharmacoepidemiology and Statistical Sciences (OpaSS)
 - Biostatistics and Post-marketing Safety
- Office of Pharmaceutical Sciences (OPS)
 - ONDQA, Generic Drugs, and Regulatory Research
- Office of Compliance

What Do We Do in CDER?

- Mission
 - CDER assures that safe and effective drugs are available to the American people
- Approvals
 - New Drug Approval
 - Over The Counter Drugs
 - Generic Drug Approval

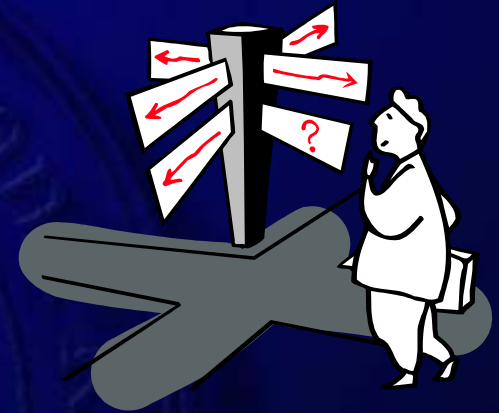
New Drug Approval: Act 505 (b)

- Substantial Evidence: The Basis for Approval
 - Evidence consisting of adequate and well-controlled investigations
 - Conducted by experts qualified to evaluate effectiveness
 - Allow conclusion that the drug will have the effect it claims



Requirement or Recommendation for New Drug Approval

- Preclinical
 - 21 CFR 312 - IND regulations
 - 21 CFR 314 - NDA regulations
 - 21 CFR 201 - Labeling regulations
- Clinical
 - 21 CFR 314 - adequate and well-controlled studies
- Guidances (FDA, ICH and Industry)
- Collaboration with review divisions - meetings, teleconference, and letters



Technical Sections

- Required to contain sufficient data to permit a knowledgeable approvability judgement
- Sections
 - Chemistry, manufacturing & controls (CMC)
 - Non-clinical pharmacology & toxicology
 - Human pharmacokinetics and bioavailability
 - Microbiology
 - Clinical
 - Statistics

Generic Drug Approval: Act 505 (j)

Brand Name Drug NDA Requirements

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

Generic Drug ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence



Main Types of CMC Submissions Reviewed

- Investigational New Drug Applications (INDs)
- Original New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)
- NDA and ANDA Supplements
- Annual Reports
- Drug Master Files (DMFs)

Supplements

- Prior Approval
- CBEs (0 and 30 days)
- Special (covered under 21 CFR 314)
 - Expedited Review
 - Catastrophic Events
 - Post Approval Changes
 - Guidance

Annual Reports



- Distribution Data
- Adverse Events
- Labeling
- Stability Data
- Changes to Official Compendia
- Additional Tests
- Narrowing of Specifications

Drug Master Files (DMFs)

Type 1: Facilities

Type 2: Drug Substance

Type 3: Containers & Closures

(screw caps, glass, bottles, syringes, rubber stoppers, etc.)

Type 4: Colors, Flavors, Excipients

Type 5: Microbiology

DMF info is proprietary and can't be disclosed to the (A)NDA holder

NDA/ANDA Review

- Components and Composition (Drug Product)
- Synthesis of the Drug Substance
- Raw Material Controls (Active & Inactives)
- Manufacturing
- Containers and Packaging Configurations
- In-Process Controls
- Finished Dosage Form Specifications and Testing
- Stability (Expiration Date)

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Evaluation of cGMPs – Inspections

- FDA's Office of Regulatory Affairs (ORA) survey and inspect regulated firms in order to assess their compliance with cGMPs.
- cGMPs - standard guidelines set out by the FDA to ensure drug development and manufacturing is carried out in safe and quality processes, to avoid contamination and ensure repeatability.

ORA District Offices

Central Region: Baltimore, Chicago, Detroit, Minneapolis, New Jersey, Philadelphia

Pacific Region: Los Angeles, San Francisco, Seattle

NE Region: New York, New England

SE Region: Atlanta, Florida, New Orleans, San Juan

SW Region: Dallas, Denver, Kansas

Total of 18 District Offices

District is responsible for conducting cGMP inspections

FDA Inspection Types

- **Pre-approval Inspection (PAI)**
 - New products (NDA & ANDA)
 - Major manufacturing/formulation changes
 - Manufacturing site changes
- **Routine Inspection**
 - cGMP compliance
- **“For Cause” Inspection**
 - Past inspection show lack of compliance
 - Suspicion of fraud

Systems Based Inspection Approach

The 6 Systems:

- Quality System
- Facilities and Equipment System
- Material System
- Production System
- Packaging and Labeling System
- Laboratory Control System

Required Qualifications & Salaries for Chemists at the FDA

- CDER Chemistry Reviewers – Usually a Ph.D. is required, although highly experienced M.S. and B.S. candidates are often considered. Salary typically ranges from GS-11 (\$54,272) for newly minted Ph.D.'s with no experience to GS-13 (\$100,554) for highly experienced Ph.D. applicants.
- ORA Inspectors/Investigators – Usually a B.S. is required. Salary typically ranges from GS-9 (\$44,856) to GS-12 (\$84,559).

Summary – Chemistry Roles in FDA Drug Approval Process

CDER CMC Reviewer

- Scientific review and analysis of data submitted in the application
- Assists in establishing specifications for manufacturing and control based on submitted data

ORA District Investigator

- Conducts inspections of manufacturing sites referenced in application
- Assure CGMP compliance, verify authenticity and accuracy of the data in applications, and report any other data which may impact firm's ability to manufacture the product in compliance with cGMPs



Thank You

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