Regulatory Affairs – Pharmaceuticals
Yale Cancer Center

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Outline

1. Introductions
2. FDA
   - Mission
   - History
   - Function
   - Structure
3. Laws, Regulations, Guidelines
4. Center for Drug Evaluation and Research (CDER)
   - Structure
   - Guidance Documents
Outline Con’t

5. Investigational New Drug Applications
6. QA-GMP, GLP, GCP
6. New Drug Application
7. Approvals
   Regular, Accelerated
8. Advisory Committees
9. Orphan Drugs
10. Pharmacovigilance
11. Advertising and Promotion
The FDA is responsible for protecting public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products medical devices, our nations food supply, cosmetics and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective safer and more affordable; and helping the public get accurate, science-based information they need to use medicines and foods to improve their health.
FDA’s History

1906  Food and Drug Act
1938 Food, Drug and Cosmetic Act
1962 Kefauver-Harris Amendment
1983  Orphan Drug Act
1984  Waxman-Hatch (Generics)
1980’s Accelerated Approvals
1990’s Pediatric Initiatives
1992-2004  PDUFA, FDAMA Review timelines
1999  Risk Management
How FDA Governs

FD&C Act
CFR
Guidelines
Guidance's
Points to Consider
Web Site  Presentations  Hearings Conferences
Laws Enforced by the FDA and Related Statutes

Federal Food, Drug, and Cosmetic Act

Additional Laws:

1957 Modernization Act (PDF 398 KB)

Administrative Procedures Act

Animal Drug User Fee Act of 2003

Best Pharmaceuticals for Children Act (PDF 76.1 KB)

Bioterrorism Act of 2002 (PDF 297 KB)

Congressional Reports Elimination Act of 1992

Controlled Substances Act

Controlled Substances Import and Export Act

Delegations of Authority to the Commissioner of Food and Drugs

Department of Education Organization Act

Related Information

Code of Federal Regulations

Federal Register

Dockets

FDA Manuals and Publications
Dietary Supplement Health and Education Act of 1994

Egg Products Inspection Act

Fair Packaging and Labeling Act

Federal Advisory Committee Act

Federal Advisory Committee Amendments

Federal Anti-Tampering Act

Federal Food and Drugs Act of 1906

Federal Fines and Sentencing Laws

Federal Import Milk Act

Federal Meat Inspections Act

Federal Trade Commission Act

Filled Milk Act

Food Quality Protection Act of 1996

Foods and Drugs


Generic Animal Drug and Patent Term Restoration Act of 1988 (Summary)
What FDA Does Not Regulate

Advertising (excluding drugs and medical devices)
Alcohol
Consumer Products
Drugs of Abuse
Health Insurance
Meat and Poultry
Pesticides
Restaurants and Grocery Stores
Water
Title 21 Food and Drugs

Part 312 Investigational New Drug Application
Part 314 Applications for FDA Approval to Market a New Drug
Part 50 Protection of Human Subjects
Part 56 Institutional Review Boards
FDA Organization

Center for Food Safety and Applied Nutrition
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Veterinary Medicine
Office of Regulatory Affairs
National Center for Toxicological Research

Acting Commissioner-Andrew von Eschenbach, MD, former Director of the NCI
FDA Organization

Center for Food Safety and Applied Nutrition

Center for Drug Evaluation and Research

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Center for Veterinary Medicine

Office of Regulatory Affairs

National Center for Toxicological Research

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NEW DRUG DEVELOPMENT

Pre-clinical Research

Clinical Studies

Accelerated Approval

Submit NDA here but with surrogate endpt

NDA Review

Post-marketing

Synthesis and Purification

Animal Testing

IND

Fast Track

Avg 5-7 yrs

Avg 6 - 7 yrs

Short-term

Long-term

Subpart E: Submit NDA here

Priority Review

NDA

Avg 1 yr

Priority 6 mo
Investigational New Drug Applications

- Traditional IND
- Emergency Use, Compassionate Use, Single Patient
- Exploratory IND
IND MUST BE SUBMITTED TO FDA BEFORE A NEW DRUG CAN BE STUDIED IN HUMANS

IND CONTENT AND FORMAT

Item 1: Cover Sheet (FDA 1571)
Item 2: Table of Contents
Item 3: Introductory Statement
Item 4: General Investigational Plan
Item 5: Investigator’s Brochure
Item 6: Protocol(s)
Item 7: Chemistry, Manufacturing & Controls
Item 8: Pharmacology & Toxicology
Item 9: Previous Human Experience
Item 10: Additional Information

SPONSOR MAY BEGIN TO INVESTIGATE THE DRUG 30 DAYS AFTER FDA HAS RECEIVED THE IND, UNLESS OTHERWISE NOTED
Name and address of sponsor

Drug name

Treatment indication

Investigators name and address

Sponsor commitment not to begin clinical investigation until IND is in effect and to adhere to all regulations
ITEM 3: INTRODUCTORY STATEMENT

Name of drug and all active ingredients
Pharmacological class
Structural formula
Dosage form (tablet, capsule, or IV)
Summary of previous human experience
Overview of objectives for proposed clinical studies
ITEM 4: GENERAL INVESTIGATIONAL PLAN

- Rationale for the drug or study
- Indication(s) to be studied
- General approach to be followed in evaluating the drug
- Clinical trials to be conducted during the next year
- Estimated number of subjects to be included in the planned clinical trials
ITEM 5: INVESTIGATOR’S BROCHURE

Brief description of chemical properties of the drug

Description of anticipated risks, side effects and special monitoring

Summaries of the pre-clinical and clinical findings describing the safety profile of the investigational drug
ITEM 6: CLINICAL PROTOCOL

Rationale for doses being studied

Statement of the objective and purpose for the study design

Inclusion/exclusion criteria

Estimation of subjects to be studied

Observations and measurements to be made

Name, address, and qualifications of investigator(s) research facility, Institutional Review Board (IRB)
Description of the Drug Substance and Drug Product

Physical, chemical, biological Characteristics

General method of preparation

Analytical methods used to assure strength, purity, identity, and quality and stability

Description of Placebo

Investigational Labels

Environmental Assessment Exemption
Dosage Form Development

- Preformulation
- Formulation
- Preliminary Stability
- Package Selection
- Formal Stability
- Manufacturing and Packaging
- Technology Transfer
Reports and Summaries supporting the planned clinical study

Pharmacology Summary

Efficiency
Pharmaceutical effect of the drug

Pharmacokinetics, Dynamics & Metabolism Summary

Description of how the drug is distributed in the body

Toxicology Summary

Description of the safety of the drug in a rodent and a non-rodent animal
TOXICOLOGY

ACUTE STUDIES
RANGEFINDING STUDIES
SUBACUTE STUDIES (1 MONTH AND 3 MONTH)
GENETIC STUDIES
SEGMENT I REPRODUCTIVE TOXICITY
SEGMENT II REPRODUCTIVE TOXICITY
SEGMENT III REPRODUCTIVE TOXICITY
CHRONIC TOXICITY (6 months, 1 year)
CARCINOGENICITY STUDIES (2 YEAR DOSING)
Pharmacokinetics/Metabolism

Absorption, Distribution, Metabolism, Elimination

Duration of Effects Versus Drug Blood Levels

Bioequivalency/ Bioavailability of alternate dosage forms

Studies in special Populations

Age

Gender

Hepatic/Renal Impaired

Drug Interaction
Item 9: Previous Human Experience

Summary of Clinical Studies with the drug

Summary of Regulatory status in the US or Internationally
  Approvals
  Withdrawal from market

Marketing History

Information on the drug from publications or other sources
Item 10: Additional Information

Drug Abuse Potential
Radioactivity of the compound
Translation of non-English documents
Any other information
## IND MAINTENANCE: AMENDMENTS

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<th>Protocol</th>
<th>Information</th>
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<td>New Protocol</td>
<td>New Toxicology</td>
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<td>New investigators</td>
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<td>Change in Protocol</td>
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<td></td>
<td>Additional technical information</td>
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IND MAINTENANCE

Safety Reports

Notify the FDA and Investigators of:

Adverse events in patients, which are serious and unexpected and related

Study results in animals suggesting a significant risk to humans

Annual Reports

Submitted within 60 days of IND anniversary date

Summarize studies and the results

Summarize Manufacturing changes

Updated Investigated Brochure

Summarize Protocol changes
Sponsor/FDA Interactions

**Formal FDA Meetings**
- Pre-IND, End of phase 2, Pre-NDA

**Verbal Communication**
- Teleconferences
- Phone conversations

**Written Correspondence**
- Secure Email
- Letters
NEW DRUG DEVELOPMENT

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Priority 6 mo

Synthesis and Purification
Animal Testing

Discovery / Screening

IND
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Phase 1

Phase 2

Short-term

Long-term

Phase 3

Fast Track
Avg 6 - 7 yrs

Subpart E: Submit NDA here
Clinical Testing

Phase 1 Normal Subjects (20-80)
  - Investigate safety as opposed to efficacy
  - Pharmacokinetics, absorption, tolerance

Phase 2-Patients with Disease (100-200)
  - Effectiveness
    - Dose ranging, optimal effect at dose strength, frequency, acceptable side effects

Phase 3-Patients with Disease (hundreds to thousands)
  - Controlled and uncontrolled Trials to determine safety and efficacy for risk benefit assessment
New Drug Application Contents

- Proposed Physicians Insert
- Pharmacological Class & Scientific Rationale
- Foreign Marketing History
- Chemistry, Manufacturing and Controls
- Nonclinical Pharmacology and Toxicology
- Human Pharmacokinetics and Bioavailability
- Microbiology
- Clinical Data
- Statistical Data
- Case Report Tabulations
- Patent and Marketing Exclusivity
NDA Clinical Data

Background/Overview of clinical Investigations
Clinical Pharmacology
Controlled and Uncontrolled Clinical Trials
Integrated Summary of Effectiveness (ISE)
Integrated Summary of Safety (ISS)
Benefits/risks
Statistical Section
Patient Profiles
Expedited Development and Review

Subpart E

Accelerated Approval (Subpart H)

Priority Review

Fast Track

Special Protocol Assessment
US Regulatory Options

Accelerated Approval

- Serious or life threatening diseases
- Surrogate endpoint may be used*
- Surrogate must be reasonably likely to predict clinical benefit
- Drug must provide benefit over available therapy
- Post market studies must verify clinical benefit
- 65 drugs/indications approved since March 1996

*Substantial evidence from well controlled clinical trials regarding the surrogate endpoint
Fast Track Status

Facilitate development (meetings, protocol review)
Expedite Review (Priority or accelerated approval)
Treat serious or life-threatening conditions
Unmet medical need
May be based on a surrogate endpoint or clinical benefit
Post-approval validation of surrogate in clinical trials and submission of advertising and promotional materials
US Regulatory Options

Priority Review

- Significant Improvement compared to marketed products
- Benefit – FDA review time $\leq 6$ months
- 52% of the 31 NME approved in 2004, 100% (4) in oncology

Special Protocol Assessment (SPA)

- Assessment of protocol meeting scientific and regulatory requirements
- Benefit-Agreement in writing, may not be changed unless substantial scientific issue is identified
Millennium – Velcade (bortezomib), Multiple Myeloma
Fast Track, Accelerated Approval, Priority Review

2001 2002 2003 2004 2005

3 Phase 1 monotherapy dose ranging studies (total n = 123)

Pivotal Phase 2, MM, n = 202

Phase 2, MM, n=54

Pre-NDA Mtg

Fast Track

EoP2 Mtg

NDA filed, 1/22/03,
NDA approved 5/13/03

Total exposure 379 patients

Phase 3, Velcade vs Dex superiority trial, n ~612

IND to approval: 5 years

Indication: refractory multiple myeloma
Orphan Drug Application

Orphan Drug Act 1984

Unmet medical need that affects less than 200,000 people

Benefits

Seven years of marketing exclusivity

Reduced filing fees

Protocol assistance and R &D support
Advisory Committees

External Advisors to FDA on Policy and Drug Approvals

Panel includes:

Physicians from Academia
Biostatisticians
Industry Representative
Pediatric Physician
Consumer Representative
Advertising and Promotion of Drugs

Unapproved Drugs - Can’t promote safety or effectiveness of drugs

Approved drugs - FDA assures Ads are not false and misleading

The package insert (labeling) serves as the basis

Product advertisements - Fair balance, Brief Summary

Reminder ads

Helpseeking ads

Continuing medical education

Off label dissemination of reprints

Comparative claims