Introduction to the Structure, Function and Process of the Food and Drug Administration

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Introduction
What is the FDA?
What Does the FDA Regulate?
Structure / Organization of the FDA
History / Legislative History of the FDA
Drug Development and the FDA Drug Approval Process
  Preclinical Development
  IND Submission
  Clinical Development – Phases I, II & III Clinical Trials
  New Drug Application (NDA)
  FDA Meetings
  Post-Marketing Surveillance
FDA Medical Device Regulation
  Pre-Market Approval (PMA)
Comparison of Drug vs. Medical Device Approvals
Expedited Drug Approval Pathways
Bibliography
Objective of Presentation

• Provide a concise overview of the Food and Drug Administration (FDA):
  - Organization
  - Responsibilities
  - Process of product approval
    - “New Drug”
    - Medical Devices

• Based on information from:
  - FDA Web site
  - Published literature
  - Direct personal experience
What is the FDA?

• Food and Drug Administration is a science-based regulatory agency within the U.S. Department of Health and Human Services (HHS) – Food and Drug Administration Act of 1988

• Led by a Commissioner of Food and Drugs appointed by the President with advice/consent from the Senate - (Current Commissioner: Margaret A. Hamburg, MD – since May 2009)

• Consists of the Office of Commissioner and 4 Directorates overseeing the core functions of the agency – Medical Products & Tobacco; Foods and Veterinary Medicine; Global Regulatory Operations and Policy; and Operations

• Organized by product area

• Location: White Oak Campus, Montgomery County, MD - 10903 New Hampshire Avenue, Silver Spring, MD 20993
Important Facts About the FDA?

- Estimated 14,648 Employees (Requested FY 2013)
- Physicians, Clinical Pharmacologists, Toxicologists, Chemists, Microbiologists, Statisticians, Other Scientific Professionals, Lawyers, Analysts, Administrative, etc.
- FDA-regulated products account for about 25 cents of every U.S. dollar ($) spent by American consumers each year
- Critical component to the success of U.S.’ public health, health care systems and economy
- FDA has 223 Field Offices (2011 data) and 13 Field Laboratories in the U.S.
- Estimated Annual Budget of $4.486 Billion (Requested FY 2013)
Mission of the FDA

- FDA is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, medical devices, most of our nation’s food supply, all cosmetics, dietary supplements, and products that emit radiation, and by regulating the manufacture, marketing, and distribution of tobacco products.

- FDA is also responsible for advancing the public health by helping to speed product innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate science-based information they need to use medicines, and to reduce tobacco use to improve health.
FDA Applies and Advances Regulatory Science

• Science-based regulatory agency, hence, applies best possible science to its core regulatory activities of protecting consumers – from pre-market review of efficacy and safety to post-market product surveillance to review of product quality

• FDA has developed a strategic plan for regulatory science - identifies 8 priority areas of regulatory science where new or enhanced engagement is essential to the continued success of FDA’s public health and regulatory mission

• Regulatory science – the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products
What Does FDA Regulate?

Foods
- safety and truthful labeling of all foods including dietary supplements
- venison and other game meat
- bottled water
- food additives
- infant formulas

Human Prescription and Non-prescription Drugs
- safety, effectiveness, quality, and labeling
- manufacturing standards

Vaccines, Blood Products, and Other Biologics
- product and manufacturing establishment licensing
- safety of the nation’s blood supply
- research to establish product standards and develop improved testing methods
What Does FDA Regulate?

Medical Devices
- from simple tongue depressors to complex technologies such as heart pacemakers
- pre-market approval of new devices
- manufacturing and performance standards
- tracking reports of device malfunctioning and serious adverse events

Electronic Products
- products that emit radiation, e.g., microwave ovens and x-ray equipment
- radiation safety performance standards for microwave ovens, television receivers
- diagnostic x-ray equipment, cabinet x-ray systems (e.g., baggage x-rays at airports)
- ultrasonic therapy equipment, mercury vapor lamps, and sunlamps
- accrediting and inspecting mammography facilities
What Does FDA Regulate?

Cosmetics
• safety
• labeling

Veterinary products
• livestock feeds
• pet foods
• veterinary drugs and devices
• veterinary biologics not regulated by USDA are considered new animal drugs

Tobacco Products
What Does FDA Regulate?

Shared Responsibility With Other Government Agencies

Pesticides
- FDA
- U.S. Department of Agriculture (USDA)
- Environmental Protection Agency (EPA)

Water
- FDA regulates labeling and safety of bottled water
- EPA develops national standards for drinking water from municipal water supplies
What FDA Does Not Regulate

Advertising (FTC)
- except for prescription drugs, medical devices, and tobacco products

Alcoholic Beverages (ATF)

Consumer Products (CPSC)
- such as paint, child-resistant packages, baby toys, and household appliances (except for those that emit radiation)

Illegal Drugs of Abuse (DEA)
- such as heroin and marijuana

Health Insurance (CMS)
- Medicare/Medicaid

Meat and Poultry (USDA)
- except for game meats, such as venison, ostrich and snake

Restaurants and Grocery Stores (State, Local, Territorial & Tribal Agencies)

Vaccines for Infectious Animal Diseases
Office of Medical Products and Tobacco

- Provides advice and counsel to the Commissioner on all medical product and tobacco-related programs and issues
- Provides high-level coordination and leadership across the centers for drug, biologics, medical devices, and tobacco products
- Oversees the agency's medical programs

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Tobacco Products
- Office of Special Medical Programs
- Office of Combination Products
- Office of Good Clinical Practice
- Office of Pediatric Therapeutics
- Office of Orphan Products Development – promoting the development of promising products for the diagnosis or treatment of rare diseases or conditions
Center for Drug Evaluation and Research (CDER)

- Ensures that safe and effective drugs are available to improve the health of people in the United States

- Regulates over-the-counter (OTC) drugs, prescription drugs, including biological therapeutics, and generic drugs (Includes: fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreens are all considered “drugs”)

- Has 19 clinical divisions organized by therapeutic area (under Office of New Drugs)
Structure / Organization of the FDA

Center for Drug Evaluation and Research (CDER)

Office of New Drugs

- Office of Antimicrobial Products (OAP)
  - Division of Anti-Infective Products (DAIP)
  - Division of Transplant and Ophthalmology Products (DTOP)
  - Division of Antiviral Products (DAP)
- Office of Drug Evaluation I
  - Division of Cardiovascular and Renal Products (DCaRP)
  - Division of Neurology Products (DNP)
  - Division of Psychiatry Products (DPP)
- Office of Drug Evaluation II
  - Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
  - Division of Metabolism and Endocrinology Products (DMEP)
  - Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
- Office of Drug Evaluation III
  - Division of Dermatology and Dental Products (DDDP)
  - Division of Gastroenterology and Inborn Errors Products (DGIEP)
  - Division of Bone, Reproductive and Urologic Products (DBRUP)
Structure / Organization of the FDA

Center for Drug Evaluation and Research (CDER)

Office of New Drugs

• Office of Drug Evaluation IV
  o Division of Medical Imaging Products (DMIP)
    ▪ Radioactive Drug Research Committee (RDRC) program
  o Division of Nonprescription Clinical Evaluation
  o Division of Nonprescription Regulation Development
  o Botanical Review Team

• Office of Hematology and Oncology Drug Products
  o Division of Oncology Products 1 (DOP 1)
  o Division of Oncology Products 2 (DOP 2)
  o Division of Hematology Products (DHP)
  o Division of Hematology Oncology Toxicology (DHOT)
Center for Biologics Evaluation and Research (CBER)

- Regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act

- Protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them

- Provides the public with information to promote the safe and appropriate use of biological products
Structure / Organization of the FDA

Center for Biologics Evaluation and Research (CBER)

- Office of the Center Director
- Office of Management
- Office of Compliance and Biologics Quality
- Office of Blood Research and Review
- Office of Vaccines Research and Review
- Office of Communication, Outreach and Development
- Office of Biostatistics and Epidemiology
- Office of Cellular, Tissue and Gene Therapies
Structure / Organization of the FDA

Center for Devices and Radiological Health (CDRH)

Responsible for protecting and promoting the public health by:

• Assuring that patients and providers have timely and continued access to safe, effective, and high quality medical devices and safe radiation-emitting products

• Providing consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee

• Facilitating medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

• Seeking to continually improve its effectiveness in fulfilling its mission by planning strategically and regularly monitoring its own progress
Structure / Organization of the FDA

Center for Devices and Radiological Health (CDRH)

• Office of the Center Director
• Office of Communication, Education, and Radiation Programs
• Office of Compliance
• Office of Device Evaluation
• Office of In Vitro Diagnostics and Radiological Health
• Office of Science and Engineering Laboratories
• Office of Surveillance and Biometrics
• Office of Management Operations
Structure / Organization of the FDA

Center for Devices and Radiological Health (CDRH)

Office of Device Evaluation
- Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
- Division of Cardiovascular Devices
- Division of Ophthalmic and Ear, Nose and Throat Devices
- Division of Neurological and Physical medicine Devices
- Division of Orthopedic devices
- Division of Surgical Devices
- Division of Reproductive, Gastro-Renal, and Urological Devices

Office of In Vitro Diagnostics and Radiological Health
- Division of Program Operations and Management
- Division of Chemistry and Toxicology Devices
- Division of Immunology and Hematology Devices
- Division of Microbiology Devices
- Division of Radiological Health
- Division of Mammography Quality Standards
1906 - The original “Pure Food and Drugs Act” is passed by Congress on June 30, 1906 and signed into law by President Theodore Roosevelt
  • FDA is at the Bureau of Chemistry, U.S. Department of Agriculture
  • Head is Chief Chemist, Dr. Harvey Washington Wiley

1940 - FDA transferred from the Department of Agriculture to the Federal Security Agency, with Walter G. Campbell appointed as the first Commissioner for Food and Drugs

1953 - Federal Security Agency becomes the department of Health, Education, and Welfare (HEW)

1988 - Food and Drug Administration Act of 1988 officially establishes FDA as an agency of the Department of Health and Human Services
  • Commissioner appointed by the President with advice/consent of the Senate
  • Broadly spells out responsibilities of the secretary and the Commissioner
Legislative History of the FDA

Some Important Milestones

1906 - The original “Pure Food and Drugs Act” prohibited interstate commerce in misbranded and adulterated foods, drinks and drugs

1938 – Federal Food, Drugs, and Cosmetic Act
   • Requires new drugs to be shown to be SAFE before marketing approval
   • Extends control to cosmetics and therapeutic devices

1951 – Durham-Humphrey Amendment – defines prescription versus nonprescription drugs

1962 – Kefauver-Harris Drug Amendments - requires new drugs to be shown to be EFFECTIVE before marketing approval


1976 – Medical Device Amendments – requires manufacturers to register with FDA and follow quality control procedures + devices classified into 3 categories which determine approval process
Legislative History of the FDA

Some Important Milestones

1984 – Drug Price Competition and Patent Term Restoration Act – permits FDA to approve applications to market generic versions of brand-name drugs without repeating studies done to prove safety and efficacy

1990 – Safe Medical Devices Act – requires manufacturers to conduct post-marketing surveillance on permanently implanted devices + authorized FDA to order device product recalls and other actions

1992 – Prescription Drug User Fee Act (PDUFA) – requires drugs and biologics manufacturers to pay fees for product applications, supplements and other services

1997 – Food and Drug Administration Modernization Act (FDAMA) – mandates wide-ranging reforms including measures to accelerate review of devices; and to regulate advertising of unapproved uses of approved drugs and devices

2002 – Medical Device User Fee and Modernization Act – requires sponsors of medical device applications to be assessed user fees for evaluation; establishes device facility inspections
Legislative History of the FDA

Some Important Milestones

2012 – Food and Drug Administration Safety and Innovation Act (FDASIA):

• Establishes a new user fee program for generic drugs - Generic drug User Fee Amendments of 2012 (GDUFA)
• Establishes a new user fee program for biosimilar biological products - Biosimilar User Fee Act (BsUFA)
• Gives FDA new expedited drug development tool – “breakthrough therapy designation” – for assisting sponsors in expediting the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases
FD&C Act

• federal law enacted by congress
• along with other federal laws, establishes the legal framework within which FDA operates
• establishes the basic framework and essential principles of new drug approval
• identifies broad criteria that new drugs must meet to gain market approval:
  “Must be subject of an FDA-approved new drug application (NDA), which must contain adequate data and information on the drug’s safety and ‘substantial evidence’ of the product’s effectiveness”
• grants FDA the authority to interpret, implement and enforce the Act including what constitutes ‘substantial evidence’ for each new drug
FDA Regulations and FDA Guidance

FDA Regulations

• Developed by the FDA based on the laws set forth in the FD&C Act or other laws under which FDA operates

• FDA follows the procedures required by the Administrative Procedure Act (another federal law) – “notice and comment rulemaking” to issue FDA regulations. This allows for public input before FDA issues a final regulation

• FDA regulations are federal laws, are not part of the FD&C Act, and can be found in Title 21 of the Code of Federal Regulations (CFR)

FDA Guidance

• Describes the agency’s current thinking on a regulatory issue

• Guidance is not legally binding on the public or FDA

• FDA follows its “Good Guidance Practice” regulation to issue FDA Guidance - the Good Guidance Practice regulation can be found at 21 CFR 10.115
New Drug Development and FDA Approval Process
“New Drug”

FDA Definition

• Any drug that is not recognized among experts, qualified by scientific training and experience, as being safe and effective under the conditions recommended for its use

• New chemical entities (NCE)

• Change in formulation, manufacture, combination of approved drugs

• New dosage schedule or regimen, new route of administration, new dosage form
FDA New Drug Application/Approval Types

- **New Drug Application (NDA) – 505(b)(1) NDA**
  - Inventing a new drug

- **New Drug Application (NDA) – 505(b)(2) NDA**
  - Modifying a new drug

- **Abbreviated New Drug Application (ANDA) – 505(j)**
  - Copying a new drug
  - Generic drug development
New Drug Development and FDA Approval Process

Steps in New Drug Development/FDA Approval process

- Identification of potentially useful compounds
- Preclinical research / development
- IND filing / FDA review / approval
- Clinical testing (Phases I, II & III clinical trials)
- NDA filing / FDA review / approval
- Marketing, Post-Marketing Surveillance and Phase IV clinical trials
New Drug Development and FDA Approval Process

New Drug Development and FDA Approval Process

Synthesis & Purification

• Identification of new molecules:
  - Inhibit or stimulate an important enzyme
  - Alter a metabolic pathway
  - Change cellular structure

• Sources of new molecules:
  - Artificial synthesis
  - Extraction from natural sources
  - Computer-generated
New Drug Development and FDA Approval Process

Biological Screening & Pharmacological Testing

• Explore pharmacological activity and therapeutic potential of new molecules:
  - Isolated cell cultures and tissues
  - Animals
  - Enzymes
  - Cloned receptor sites

• Identify versions of new molecules:
  - Highest level of pharmacological activity
  - Most therapeutic potential
  - “Lead compounds”
New Drug Development and FDA Approval Process

Pharmaceutical Dosage Formulation, Bioanalytical Method Development & Stability Testing

• Turn active compound (drug substance) into form and strength suitable for human use

• Dosage forms - tablets, capsules, liquids, ointments, sprays, patches, etc.

• Dosage strengths - 50, 100, 250, 500 mg, etc.

• Final formulation (Drug Product) = drug substance + excipients

• Define and characterize bioanalytical method – for quantification of the drug candidate in biological fluids

• Initiate stability testing of drug substance and drug product (final formulation)
New Drug Development and FDA Approval Process

Toxicology & Safety Testing

• Evaluate toxic and pharmacologic effects in animals – to establish potential risk to man + estimate first human dose

• Short-term studies: 2 weeks to 3 months
  - Safety pharmacology studies – CVS, CNS, respiratory, renal systems
  - Genotoxicity studies – battery of 3 studies
  - 4-week toxicity study in rats (acute toxicity)
  - 4-week toxicity study in dogs (acute toxicity)
  - Dose-range finding reproductive toxicity studies (Segments I, II & III in rats and Segment II in rabbits)
  - 13-week pre-oncogenicity study in rats
  - 13-week pre-oncogenicity study in mice
  - Dose-range finding – transgenic mice study (28-day)

• Submit carcinogenicity protocols to: Carcinogenicity Assessment Committee (CAC) for review and concurrence – 45-day Special Protocol Assessment (SPA)
New Drug Development and FDA Approval Process

Toxicology & Safety Testing

- Long-term studies: few weeks to 2 years
  - 6-month chronic toxicity study in rats
  - 9-month chronic toxicity study in dogs
  - Definitive reproductive toxicity studies (Segment I, II & III in rats + Segment II in rabbits)
  - 104-week carcinogenicity study in rats
  - 104-week carcinogenicity study in mice
  - 6-month transgenic mice study (Tg.Ac or p53)
  - Toxicokinetic studies – ADME – as part of chronic toxicity studies

- Additional toxicology studies may be required
  - special toxicity studies

- Toxicology studies must be conducted under GLP guidelines
  - established June 1979 - established standards for nonclinical lab’s organization and personnel, physical structure, equipment and operating procedures
# New Drug Development and FDA Approval Process

## Duration of Repeated Dose Toxicity Studies to Support Phase I, II, and III Clinical Trials in the United States

<table>
<thead>
<tr>
<th>Duration of Clinical Trials</th>
<th>Minimum Duration of Repeated Dose Toxicity Studies</th>
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<tbody>
<tr>
<td></td>
<td>Rodents</td>
</tr>
<tr>
<td>Single Dose</td>
<td>2 - 4 Weeks(^1)</td>
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<tr>
<td>Up to 2 Weeks</td>
<td>2 - 4 Weeks(^1)</td>
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<tr>
<td>Up to 1 Month</td>
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<tr>
<td>Up to 3 Months</td>
<td>3 Months</td>
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<tr>
<td>Up to 6 Months</td>
<td>6 Months</td>
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<tr>
<td>&gt; 6 Months</td>
<td>6 Months</td>
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Source: FDA M3 ICH Guidance, July 1997
Investigational New Drug (IND) Submission

• Application – filed with FDA at the end of a successful pre-clinical development program for a new drug – to obtain permission to conduct clinical studies with the investigational drug

• Legally, to seek exemption from the federal statute to ship the investigational drug across state lines to study sites

• Primary objective of the IND application process is to protect clinical trial subjects from unnecessary risks

• Types of INDs:
  - Sponsor-INDs (Commercial-INDs)
  - Investigator-INDs (Research-INDs)
  - Emergency Use-INDs (Compassionate Use- or Single-patient INDs)
  - Treatment-INDs
  - Screening-INDs
## IND Content and Format [Section 21 CFR 312.23]

<table>
<thead>
<tr>
<th>Section</th>
<th>Content – 3 Copies</th>
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<tbody>
<tr>
<td>1</td>
<td>Cover Sheet (FDA Form-1571) [21 CFR 312.23(a)(1)]</td>
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<td>2</td>
<td>Table of Contents [21 CFR 312.23(a)(2)]</td>
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<td>3</td>
<td>IND Introductory Statement [21 CFR 312.23(a)(3)]</td>
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<td>4</td>
<td>General Investigational Plan [21 CFR 312.23(a)(3)]</td>
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<td>5</td>
<td>Investigator's Brochure [21 CFR 312.23(a)(5)]</td>
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<td>6</td>
<td>Protocols [21 CFR 312.23(a)(6)]</td>
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<tr>
<td>7</td>
<td>Chemistry, Manufacturing, and Control Information [21 CFR 312.23(a)(7)]</td>
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<td>8</td>
<td>Pharmacology and Toxicology Information [21 CFR 312.23(a)(8)]</td>
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<tr>
<td>9</td>
<td>Previous Human Experience with the Investigational Drug [21 CFR 312.23(a)(9)]</td>
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<tr>
<td>10</td>
<td>Additional Information [21 CFR 312.23(a)(10)]</td>
</tr>
<tr>
<td>11</td>
<td>Relevant Information [21 CFR 312.23(a)(11) and (b), (c), (d), and (e)]</td>
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New Drug Development and FDA Approval Process

Guidance Documents to Help Prepare INDs:

• Guidance for clinical investigators, sponsors, and IRBs: investigational new drug applications (INDs) — determining whether human research studies can be conducted without an IND (Issued 9/2013)

• Enforcement of Safety Reporting Requirements for INDs and BA/BE Studies (PDF - 41KB) (Issued 6/6/2011)

• CGMP for Phase 1 Investigational Drugs (PDF – 132KB) (Issued 7/2008)

• Exploratory IND Studies (PDF – 220KB) (Issued 1/12/2006)

• Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (PDF – 42KB) (Issued 11/1995)

• Q & A - Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products  (Issued 10/2000)


• IND Exemptions for Studies of Lawfully Marketed Drugs or Biological Products for the Treatment of Cancer (PDF – 188KB)  (Issued 1/2004)

• Guidance for Drug Master Files

• Required Specifications for FDA’s IND, NDA, and ANDA Drug Master File Binders


• Safety Reporting Requirements for INDs and BE/BA Studies  (Issued 9/28/2010)
FDA’s Review of the IND

• FDA performs safety review of IND within 30 days at the appropriate CDER Division

• Review is team- and discipline-based and focuses on:
  - Pharmacology/toxicology review – by reviewing pharmacologist
  - Chemistry review – by reviewing chemist
  - Clinical review – reviewing medical officer

• Outcome:
  - Administrative silence / No contact within 30 days = Sponsor may initiate clinical trial (= IND Active)
  - Clinical Hold – if safety concerns; serious deficiencies; IND has insufficient information to assess risks to subjects, investigator unqualified, misleading IB, etc.
  - To clear the clinical hold, IND holder must respond to the safety concerns, and/or deficiency letters and/or information request letters

• Sponsor must request 45-day SPA – for study design comments
New Drug Development and FDA Approval Process

Clinical Testing (GCP): The Clinical Trial Process

- Planning
- Protocol + Informed Consent
- Sites prequalification
- Investigators’ Meeting / Site initiation
- Institutional Review Board (IRB) – protocol submission/approval
- Submit protocol to the IND ± request 45-day SPA
- Recruitment / screening / randomization of subjects
- Follow-up visits / CRFs completion
- Monitoring & auditing of sites
- Site close-out visits
- Database lock / Statistical analysis / Clinical trial report writing
Phase I Clinical Trials

- Entry-into-man (first-in-man, first-in-human) studies
- Evaluate the safety and pharmacological effects of new drug at anticipated therapeutic range
- 20 - 80 normal healthy human volunteers
- Cancer, HIV/AIDS patients
- Study ADME patterns (PK); preferred route of administration; side effects of various doses; establish safe dosage range (and MTD); and mechanism of action
- Duration - 6 months to 1 year
- Only 70% of submitted INDs reach Phase I Clinical trials
Phase II Clinical Trials

- Evaluate additional safety, tolerability and initial efficacy
- 50 - 300 patient volunteers with the disease / symptoms new drug is intended to treat
- Provide data for the design of the Phase III clinical trials – for sample size calculation, dose selection, need for titration, clinical endpoints, etc.
- End-of-Phase II FDA meeting – to discuss Phase III plans
- Duration: about 2 years
- Only 33% of new drugs complete Phase II clinical trials
Phase III Clinical Trials / Registration Trials

- Assess effectiveness and safety and the appropriate dose/dosage range for the drug – for the specific indication

- Large trials - several hundred to several thousand patients with the disease (1000-3000)

- Two positive well controlled clinical trials + 1 long-term safety trial (≥1 year) for collection of ICH safety data

- In outpatients and hospital settings

- Early experience to practicing physicians as in post-approval use

- Duration: ≥3 years

- Only 27% of new drugs complete Phase III clinical trials

- Pre-NDA FDA Meeting – after completing all Phase III clinical trials
New Drug Development and FDA Approval Process

Pre-NDA FDA Meeting

• Inform FDA about intent to file an NDA

• Present summary of evidence for efficacy and safety of the product

• Obtain FDA concurrence on the NDA filing

• Obtain FDA concurrence on the format and presentation of data
New Drug Development and FDA Approval Process

New Drug Application (NDA) Submission

- Application for approval to market a new drug in the U.S.
  - 505(b)(1) application
  - 505(b)(2) application

- Submit NDA to CDER Document Room

- Filing Review by reviewing Division - must respond to sponsor within 60 days to indicate decision to file or not
  - Division - 45 day meeting
  - Is NDA complete or incomplete?
  - If complete – standard or priority review?

- Incomplete / deficient NDA – Refuse-to-file letter

- Complete – initiates primary review of NDA and review clock starts
  - Acknowledgement letter to sponsor
  - Priority review – 6 months
  - Standard review – 10 months
## Contents of FDA’s New Drug Application (NDA) for a Drug/Biologic Intended for Marketing for Human Use

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<th>Section</th>
<th>Content</th>
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<td>Index</td>
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</table>
| 2       | Labeling:  
Draft Labeling; or  
Final Printed Labeling |
| 3       | Summary [21 CFR 314.50 (c)] |
| 4       | Chemistry Section:  
A. Chemistry, manufacturing, and controls information [e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2]  
B. Samples [21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)] [Submit only upon FDA's request]  
C. Methods validation package [e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2] |
| 5       | Nonclinical pharmacology and toxicology section [e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2] |
| 6       | Human pharmacokinetics and bioavailability section [e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2] |
| 7       | Clinical microbiology section [e.g., 21 CFR 314.50(d)(4)] |
| 8       | Clinical data section [e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2] |
| 9       | Safety update report [e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2] |
| 10      | Statistical section [e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2] |
| 11      | Case report tabulations [e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2] |
| 12      | Case report forms [e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2] |
| 13      | Patent information on any patent that claims the drug/biologic [21 U.S.C. 355(b) or (c)] |
| 14      | A patent certification with respect to any patent that claims the drug/biologic [21 U.S.C. 355 (b)(2) or (j)(2)(A)] |
| 15      | Establishment description [21 CFR Part 600, if applicable] |
| 16      | Debarment certification [FD&C Act 306 (k)(1)] |
| 17      | Field copy certification [21 CFR 314.50 (l)(3)] |
| 18      | User Fee Cover Sheet [PDUFA Form FDA 3397, GDUFA Form FDA 3794, BsUFA Form FDA 3792, or MDUFMA Form FDA 3601] |
| 19      | Financial Disclosure Information [21 CFR Part 54] |
| 20      | Other [Specify] |
NDA Review Process & Approval

• Drug safe and effective for proposed use(s) – benefits outweigh risks?

• Proposed labeling appropriate? If not, what should it contain?

• Drug manufacturing methods and controls adequate to preserve drug’s identity, strength, quality, and purity?

• Team- and discipline-based primary review process:
  ▪ Medical/clinical reviewer
  ▪ Pharmacology/toxicology reviewer
  ▪ Chemistry reviewer
  ▪ Biopharmaceutics reviewer
  ▪ Microbiology reviewer
  ▪ Statistical reviewer
  ▪ Public Advisory Committee meeting
  ▪ Proposed labeling review

• Preapproval inspections of:
  ▪ Selected clinical trial sites
  ▪ Sponsor’s manufacturing facilities
• Formal Action Letters on NDAs:
   Approval letter
   Approvable letter – minor deficiencies, labeling changes, post-approval commitment(s)
   Not approvable letter – lists deficiencies and reason for decision
Post-approval Activities

• Post-marketing surveillance

• Phase IV clinical trials may be conducted to:
  • Reveal additional side-effects, serious and unexpected adverse drug effects, drug interactions
  • investigate possible new therapeutic uses, additional dosage strengths, dosing regimen, dosage forms or other route of administration
  • Regulatory mandate – condition for market approval

• Special population studies – elderly, pregnant women, kidney failure, children, etc.
Results/Facts About New Drug Development

- 5,000 - 10,000 compounds screened for pharmacological activity
- 5 enter clinical trials
- 1 makes it to the market
- 12 - 15 years later
- $1.2 billion
Basic Regulatory Requirements for Medical Devices in the U.S.

- Establishment registration

- Medical device listing

- Premarket notification 510(K)
  - 510(K) devices must demonstrate substantial equivalence to a device legally in commercial distribution in the U.S. before May 28, 1976; or
  - to a device that has been determined by the FDA to be substantially equivalent

- Premarket approval (PMA)
  - Required by high risk devices with significant risk of illness or injury
  - Devices found not substantially equivalent to class I or II predicate through the 510(K) process
  - Requires the submission of clinical data to support claims made for the device
Classification of Medical Devices

• Classified into Class I, II and III

• Class I: low to moderate risk – general controls
  ▪ Most are exempt from premarket notification 510(K)

• Class II: moderate to high risk – general controls and special controls
  ▪ Most require premarket notification 510(K)

• Class III: high risk – general controls and premarket approval (PMA)
  ▪ Most require premarket approval (PMA)

• Risk, therefore, regulatory control increases from class I to II to III
Medical Device Premarket Approval

- PMA is the medical device application that is most similar to that of a new drug
- Only few devices (2%) are approved through the PMA process
- For new devices not substantially equivalent to a predicate device:
  - Manufacturers must either submit a PMA; or
  - Petition the FDA to reclassify into a Class I or II before marketing
- PMA – problem is few new device evaluations use RCTs
Medical Device Regulation and FDA Approval Process

Medical Device Premarket Approval

• PMA – problem is few new device evaluations use RCTs due to:
  ▪ Methodological difficulties for device evaluations – randomization, appropriate and ethical control groups, measurable outcomes in a timely manner
  ▪ Federal regulations for devices
  ▪ Share volume of devices – forces FDA to prioritize its review to safety over efficacy
Medical Device Regulation and FDA Approval Process

Medical Device Premarket Approval

- File investigational device exemption (IDE) with the FDA (CDRH) to allow investigational device to be used in a clinical study to collect safety and effectiveness data to support a PMA:
  - Report of prior clinical, animal and laboratory testing with device
  - Investigational plan – protocol, monitoring procedures for the clinical study
  - Description of methods, facilities, controls used for the manufacture, processing, packing, storage and installation of the device
  - List of investigators, IRBs to be used for the clinical study
  - Inform consent form, label for the investigational device
  - Name and indication for use of the device
  - Description of the device and risk analysis

- FDA performs safety review of IDE within 30 days
Medical Device Regulation and FDA Approval Process

Medical Device Premarket Approval

• IDE Outcome:
  ▪ Administrative silence / No contact within 30 days = Sponsor may initiate clinical trial (= IDE Active)
  ▪ Clinical Hold – if safety concerns; serious deficiencies; IDE has insufficient information to assess risks to subjects, investigator unqualified, etc.
  ▪ To clear the clinical hold, IDE holder must respond to the safety concerns, and/or deficiency letters and/or information request letters

• Conduct clinical trial after FDA & IRB approval

• After clinical trial – prepare and submit PMA application to CDRH, FDA

• FDA Review of submitted PMA:
  ▪ 45 working days response time – from receipt – file ± expedited review
  ▪ Refuse to file – if serious deficiencies
  ▪ To clear the clinical hold, IDE holder must respond to the deficiencies and/or information request letters
Medical Device Regulation and FDA Approval Process

Medical Device Premarket Approval

• Complete PMA application:
  - In-depth scientific, regulatory and quality systems review by appropriate FDA personnel
  - 180-day review clock starts
  - Sponsor may request a 100-day meeting with agency to review status of application
  - FDA may seek Advisory Committee meeting and recommendation

• Final deliberations, documentation, and notification of FDA decision:
  - Approval order
  - Approvable letter
  - A not approvable letter
  - An order denying approval

• Approved – Post-marketing surveillance applies as with drugs
Comparison of Drugs vs Medical Devices

Similarities in FDA Regulation

• Manufacturers of drugs and medical devices can market products only for intended use as approved by the FDA

• Both must comply with federal regulations for labeling, advertising, production and post-marketing surveillance

• Both offer a pathway for providing products to patients for humanitarian use – Orphan drug OR Humanitarian Device Exemption

• Both allow for study of the product in humans – IND OR IDE
Differences in FDA Regulation

• FDA requires all drugs to demonstrate safety and efficacy in humans – only Class III medical devices have same requirement

• Generic drugs are required to demonstrate bioequivalence to the reference (predicate) drug - a higher standard than the substantial equivalence required for 510(K)-cleared devices

• All manufacturers of drugs must undergo FDA facility inspections – manufacturers of medical devices are often not inspected

• Overall, the drug review process is better established and much more rigorous than the medical device review process
**FDA Expedited Drug Approval Pathways – Fast Track**

- **Year Established:** 1988

- **Qualifying criteria:**
  - Drug intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR
  - Drug that has been designated as a qualified infectious disease product

- **Nature of Program:** Designation

- **When to Submit:**
  - With IND or after
  - Ideally, no later than the pre-BLA or pre-NDA meeting

- **Timeline for FDA response:** Within 60 calendar days of receipt of request

- **Features of Program:**
  - Actions to expedite development and review
  - Rolling review
### FDA Expedited Drug Approval Pathways – Accelerated Approval

<table>
<thead>
<tr>
<th>Year Established:</th>
<th>1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying criteria:</td>
<td>Drug that treats a serious condition <strong>AND</strong> generally provides meaningful advantage over available therapies <strong>AND</strong> demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</td>
</tr>
<tr>
<td>Nature of Program:</td>
<td>Approval Pathway</td>
</tr>
</tbody>
</table>
## FDA Expedited Drug Approval Pathways – Accelerated Approval

<table>
<thead>
<tr>
<th>When to Submit:</th>
<th>Discuss possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timeline for FDA response:</td>
<td>Not specified</td>
</tr>
<tr>
<td>Features of Program</td>
<td>Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit</td>
</tr>
</tbody>
</table>
Year Established: 1992

Qualifying criteria:
An application (original or efficacy supplement) for a drug that treats a serious condition AND if approved, would provide a significant improvement in safety or effectiveness OR
Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR
An application for a drug that has been designated as a qualified infectious disease product OR
Any application or supplement for a drug submitted with a priority review voucher

Nature of Program: Designation
<table>
<thead>
<tr>
<th><strong>When to Submit:</strong></th>
<th>With original BLA, NDA, or efficacy supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timeline for FDA response:</strong></td>
<td>Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement</td>
</tr>
<tr>
<td><strong>Features of Program</strong></td>
<td>Shorter clock for review of marketing application (6 months compared to the 10-month standard review)</td>
</tr>
</tbody>
</table>
**FDA Expedited Drug Approval Pathways – Breakthrough Therapy**

<table>
<thead>
<tr>
<th>Year Established:</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying criteria:</td>
<td>A drug that is intended to treat a serious condition <strong>AND</strong> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
</tr>
<tr>
<td>Nature of Program:</td>
<td>Designation</td>
</tr>
</tbody>
</table>
| When to Submit: | • With IND or after  
  • Ideally, no later than the end-of-Phase 2 meeting |
| Timeline for FDA response: | Within 60 calendar days of receipt of request |
| Features of Program | • All fast track designation features  
  • Intensive guidance on efficient drug development during IND, beginning as early as Phase 1  
  • Organizational commitment involving senior managers |
FDA web site:  http://www.fda.gov/default.htm


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