Regulatory Environment

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Contents of this presentation were developed in collaboration with Angela R. Charboneau Wishon, J.D.
Commercializing biomedical research requires meeting various requirements that are established and enforced by regulatory agencies in US and globally.
Why are the regulations written and enforced by the Food and Drug Administration?
FDA Regulatory Origin

- FDA has its “origin” with the creation of the Agricultural Division in the Patent Office in 1848
- Defined role for FDA Chemist existing within the USDA in 1862
- Pure Food and Drugs Act in 1906 authorized as a Federal Agency
“An Act for *preventing the manufacture, sale or transportation* of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for *regulating traffic therein*, and for other purposes.”
The Federal Food, Drug, and Cosmetic Act of 1938

“To prohibit the movement in **interstate** commerce of adulterated and misbranded food, drugs, devices, and cosmetics, and for other purposes.”

The authority for the FDA is founded in the Commerce Clause of the USA Constitution.
Misbranding as Drug

Source: FDA History of Drug Regulation
Evolution of Regulations

Event → Public Reaction → Legislative Action → Outrage and demands for safety → Laws and Regulations → Disaster or tragedy → Event
Progression of Regulation of Drugs, Biologicals & Devices

- 1902 Biologics Control Act
- 1906 Pure Food and Drugs Act
- 1938 Food Drug and Cosmetic Act
- 1951 Durham-Humphrey Amendment
- 1962 Kefauver Harris Amendments
- 1976 Medical Device Amendments
Progression of Regulation of Drugs, Biologicals & Devices

- **1902 Biologics Control Act**
  - Unregulated production of tetanus antitoxin; Diptheria epidemic

- **1906 Pure Food and Drugs Act**
  - Unsafe products; “The Jungle”

- **1938 Food Drug and Cosmetic Act**
  - Unsafe products; Elixir of Sulfanilamide poisonings

- **1951 Durham-Humphrey Amendment**
  - Unsafe products; compounds sold without prescription

- **1962 Kefauver Harris Amendments**
  - Thalidomide disaster

- **1976 Medical Device Amendments**
  - Excessively high radiation exposures
Progression of Regulation of Drugs, Biologicals & Devices

- 1990 Safe Medical Devices Act
- 1992 Prescription Drug User Fee Act
- Food and Drug Modernization Act (FDAMA) of 1997
- Best Pharmaceutical for Children Act 2002
- Pediatric Research Equity Act of 2003
- Food and Drug Administration Amendments Act (FDAAA) of 2007
- 21st Century Cures Act
The FD&C Act and amendments dictate the scope and responsibilities of the FDA.

- **FD&C Act**
  - resulted from public safety events or public health challenges

- The FD&C act empowers the FDA to enforce laws.
- The FDA an agency of the US government that is responsible for medical products.
Regulatory Authority

- As of 2017, FDA regulates $1 Trillion worth of **products**
- Protecting the public health by
  - assuring that foods* are safe, wholesome, sanitary and properly labeled;
  - ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective
- Protecting the public from electronic product radiation
Statement of FDA Mission

- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.

The FDA is a public health agency.
Food and Drug Administration is charged with assuring the safety, efficacy and security of:

- prescription medications
- over-the-counter pharmaceutical products
- vaccines
- biopharmaceuticals
- blood transfusions
- medical devices
- electromagnetic radiation emitting devices
- food
- tobacco products
- dietary supplements
- veterinary products
- cosmetics
Statement of FDA Mission

- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable …

- and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

The FDA is a partner in the development and use of medical products.
How are the regulatory standards set for medical products in U.S.?

The FDA establishes regulations governing the development and use of medical products.
What are “Federal Regulations?”

**Administrative Laws — Public Law**
- Passed by the Legislative Branch

**Rules and Regulations**
- Interpretation of the “Law” by the Executive Branch
- Enforceable, codified instructions
- Code of Federal Regulations (CFR)

**Guidance**
- Interpretation of Regulations to give directions and to clarify
- Recommended approach to meeting the Regulations
The rulemaking process
Regulatory Framework – Agencies

[Diagram showing various agencies and their acronyms, including USDA, DOC, DHHS, DVA, NSF, NASA, NRC, DOS, DOT, DOD, BIS, OHRP, ASH, CDC, NIH, CMS, OCR, NVPO, OLR, IHS, NVPO, OLR, NIH, CDC, CMS, OR, FDA, OHRP, DOC, DOD, DOJ, USDA, NIST, ATF, DEA, FTC, NRC, NSF, ITC, NASA, NIST, OLAW, OLR]
Regulatory Authority - Drug Package and Labels
Regulatory Authority - Advertisements

“Oh great. Now the FDA is regulating safety coated caplets of eyes of newt.”

Source: Cartoonstock.com
Regulatory Authority - Off Label Promotion

Source: Cartoonstock.com
Regulatory Authority - Increased Inspections

Source: Cartoonstock.com
Regulatory Authority – Oversight of Research

Source: Cartoonstock.com
FDA Organization

- Office of the Commissioner
- Office of Foods and Veterinary Medicine
- Office of Global Regulatory Operations and Policy
- Office of Medical Products and Tobacco
  - Center for Biologics Evaluation and Research
  - Center for Devices and Radiological Health
  - Center for Drug Evaluation and Research
  - Center for Tobacco Products
  - Office of Special Medical Programs
  - Oncology Center of Excellence
- Office of Operations
How are the regulatory standards set for medical products for markets outside the U.S.?

Different regulatory environments for drugs versus devices
Global Pharmaceutical Market

- International Conference on Harmonization
- European Medicines Agency
- Food and Drug Administration

- Marketplace is worldwide
  - Consumption
  - Production
  - Regulation
International Council (Conference) for Harmonisation

- International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
  - Established in 1990 (USA, EC, Japan)
  - Registered as international Organization in 2015, Switzerland
- Non-profit Association
- Mission: to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.
Members and Observers at ICH

- Founding Regulatory Members
  - The European Commission (EC)
  - The US Food and Drug Administration (FDA)
  - The Ministry of Health, Labour and Welfare of Japan (MHLW)

- Industry members

- Other Regulatory agencies representing:
  - Canada, Switzerland, Brazil, Rep. Korea
  - Official Observers:
    - WHO, India, Cuba, Mexico, Singapore, South Africa, Kazakhstan, Russia, Chinese Taipei, Australia,
    - Federations (Asia-Pacific Economic Cooperation, Association of Southeast Asian Nations, East African Community, Gulf Health Council, Pan American Network, Southern Africa Development Community)
Quality Guidelines
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Efficacy Guidelines
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Safety Guidelines
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Multidisciplinary Guidelines
Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).
1) Global pharmaceutical market
2) FDA regulations parallel ICH guidances
What about devices?

There is no equivalent international body for the regulatory and developmental standards for devices.

Mostly rely on engineering standards for uniformity of product development.
What standards apply?

- No single international set of standards (ICH was established for drugs)
- There are two organizations that typically issue international standards:
  - International Organization for Standardization (ISO)
  - International Electrotechnical Commission (IEC)
- Nomenclature: typically, with three parts.
  - Issuing organization
  - Number
  - Year of issue
    - For example: ISO 14971:2007 is an international standard that ISO issued in 2007.
    - The title is *Medical devices — Application of risk management to medical devices.*
International oversight of medical devices

International Medical Device Regulators Forum

- **Members:**
  - Australia, Therapeutic Goods Administration
  - Brazil, National Health Surveillance Agency (ANVISA)
  - Canada, Health Canada
  - China, China Food and Drug Administration
  - European Union, European Commission
  - Japan, Pharmaceuticals and Medical Devices Agency
  - Russia, Russian Ministry of Health
  - Singapore, Health Sciences Authority
  - USA, US Food and Drug Administration

- **Official Observers:**
  - World Health Organization
  - APEC LSIF Regulatory Harmonization Steering Committee

- **Affiliate Organizations:**
  - Asian Harmonization Working Party
  - Pan American Health Organization (PAHO)

http://www.imdrf.org/
FDA Oversight of Device Studies

- Based on regulation of interstate commerce.
- INDs and IDEs are permits that allow unapproved drugs/devices to move in interstate commerce in order to be studied.
What standards apply?

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  - Number
  - Year of issue
    - For example:
    - The title is Medical devices — Application of risk management to medical devices.
What standards apply?

- **United States**
  - American National Standards Institute (ANSI)
    - U.S. representative to ISO.
    - Contributors: Association for the Advancement of Medical Instrumentation (AAMI) and the American Society for Quality (ASQ)
  - U.S. standards examples:
    - ANSI/AAMI/ISO 13485:2003 (R2009), Medical devices — Quality management systems - Requirements for regulatory purposes
    - ANSI/AAMI/ISO 14971:2007 (R2010), Medical devices — Application of risk management to medical devices
Drug development and approval process
Who develops drugs?

- Any stakeholder who seeks approval of the FDA to conduct clinical investigations
  - (with a goal) to market a new drug
  - (with a goal) to market a therapeutic equivalent of an approved drug
  - ... of an FDA-approved drug that may or may not result in changes to the approved drug label
  - new disease, new formulation, new dose, new mode of administration, new patient population, changes in manufacturing and controls ...

... is called the “Drug Sponsor”

- **Sponsor** of an IND application is the party who submits the application to FDA. In the absence of any other sponsor (e.g. pharmaceutical company), the investigator conducting the proposed clinical investigation is the sponsor of the IND application.
Drug development process

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
- FDA Filing/Approval & Launch Preparation
Parallel activities that are critical to successful development

**Safety**
- Prototype Design or Discovery
- In vitro and animal testing
- Human and animal testing
- Safety follow-up

**Medical utility**
- In vitro and computer model evaluation
- In vitro and animal models
- Human efficacy evaluation

**Industrial-ization**
- Physical design
- Characterization and small scale production
- Manufacturing scale-up, Refined specifications
- Mass production

Parallel activities in preclinical development

Preclinical flow diagram

The parallel and inter-related activities contributing to preclinical development are summarized with color coding to denote related components:
- manufacturing (red),
- analytical (grey),
- documentation (orange),
- safety (blue),
- clinical (green).

API, active pharmaceutical ingredient;
CMC, chemistry, manufacturing, and controls;
FDA, US Food and Drug Administration;
GLP, good laboratory practice;
GMP, good manufacturing practice;
ICF, informed consent form;
IND, Investigational New Drug;
PK, pharmacokinetics.

Preclinical flow diagram. The parallel and interrelated activities contributing to preclinical development are summarized with color coding to denote related components:
- manufacturing (red),
- analytical (grey),
- documentation (orange),
- safety (blue),
- clinical (green).

API, active pharmaceutical ingredient; CMC, chemistry, manufacturing, and controls; FDA, US Food and Drug Administration; GMP, good manufacturing practice; GLP, good laboratory practice; ICF, informed consent form; IND, Investigational New Drug; PK, pharmacokinetics.

Steinmetz KL and Spack EG. The basics of preclinical drug development for neurodegenerative disease indications. BMC Neurol. 2009;12;9 Suppl S2.
Good Laboratory Practice: A Historical Perspective

- Until mid 1970s, FDA assumed that study reports accurately described study conduct and precisely reported study data.

- In 1974 – 1975, FDA reviewed facilities and found serious deficiencies.

- Good Laboratory Practice (GLP) regulations developed to ensure quality of data and studies.
Good Laboratory Practice

▪ “Prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research of marketing permits for products regulated by the Food and Drug Administration.”

▪ Does not apply to “basic exploratory studies carried out to determine if a test article has any potential utility or to determine physical or chemical characteristic of a test article.”

▪ [Code of Federal Regulations, Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies]
Good Laboratory Practices (GLP)

- FDA Regulatory Requirement (21 CFR Part 58)
- “Good Laboratory Practices for Nonclinical Laboratory Studies”
  - FDA Regulations at 21 CFR Part 58
  - Data intended to support application for research or marketing permits for products regulated by FDA
  - Compliance intended to assure the quality and integrity of the safety data filed [to FDA for other applicable sections of Title 21]
GLP Regulatory Requirements

- Key Areas:
  - Organization and Personnel
  - Facilities and Operation of Facilities
  - Equipment
  - Test and Control Articles
  - Protocol for and Conduct of Nonclinical Laboratory Study
  - Records and Reports
  - Disqualification
GLP Regulatory Requirements

- **Goal:** Data can be traced back to source and SOP adherence key areas
  - Replication
  - Validation
  - Documentation

- **Active Monitoring**
  - FDA Inspections prior to work beginning
  - Organization Quality Assurance ongoing
  - FDA Inspections routinely
Differentiation

GLP

Test Facility Management

Archivist

Feed Mixtures

Animal Care

Histology

Bioanalytics

Test Facility Management

Study Director

Analysis of Test item and "Specimen"

• Approved Study Plan
• Master Schedule
• Final Report(s)

Analytical Lab

• Suitable Facilities
• Qualified Personnel
• Qualified Equipment
• Validated Test Methods
• Approved Test Instructions
• SOPs
• Documentation, Raw data, Archiving

Batch Release

BRR

Self Inspection

Control of Raw materials and Products

• Identity
• Purity
• Content
• CU
• Stability

Pharmaceutical Manufacturer

Qualified Person

Production, Packaging, Storage

Source: RAPS 2005 Annual Meeting
Regulations Along the Drug Life

Not Regulated

GLP
21 CFR 11
Electronic Records & Signatures

GCP
IND Submission & Review
BLA/NDA Submission & Review

GMP
Post Marketing Surveillance

Safety, Quality, Efficacy

Basic Research
Drug Discovery
Preclinical Development
Clinical Trials Phase I, II, III
Manufacturing incl. APIs QC Laboratories

Lead to Drug Target

GLP = Good Laboratory Practices
GMP = Good Manufacturing Practices
GCP = Good Clinical Practices

GxP = GLP+GCP+GMP = Predicate Rules
IND = Investigational New Drug Application
BLA = Biologic License Application
NDA = New Drug Application
Parallel activities that are critical to successful development

Parallel activities that are critical to successful development

**Safety**
- Prototype Design or Discovery
- In vitro and animal testing
- Human and animal testing
- Safety follow-up

**Medical utility**
- In vitro and Computer model evaluation
- In vitro and animal models
- Human efficacy evaluation

**Industrialization**
- Physical design
- Characterization and small scale production
- Manufacturing scale-up
- Refined specifications
- Mass production

Challenges of CMC: from Early Development through the Product Life Cycle

Where does CMC fit in the Product Development Cycle?

Product development process and milestones

FROM: Michael V.W. Bergamini, Ph.D.
Chief Scientific Officer / Executive Vice President; Nicox Ophthalmics, Inc.
Adjunct Professor, Pharmacology and Neuroscience; University of North Texas Health Science Center at Fort Worth
Good Clinical Practices (GCP)

- GCP is the minimum standard for design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials.

- Regulatory/Guidance Requirements:
  - Protection of Human Subjects (21 CFR Part 50)
  - Institutional Review Boards (21 CFR Part 56)
  - Electronic Records; Electronic Signatures (21 CFR Part 11)
  - (21 CFR Part 312)
  - International Council for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH GCP E6)

*Note there are slight variations between ICH and FDA Regulations*
ICH GCP Requirements

- Key Areas of ICH GCP E6:
  - Glossary
  - Principles of ICH GCP
  - IRB
  - Investigator
  - Sponsor
  - Clinical Trial Protocol and Protocol Amendments
  - Investigator’s Brochure
  - Essential Documents for Conduct of a Clinical Trial
GCP Regulatory Requirements

- Key Areas of FDA GCP:
  - IRB
  - Investigator
  - Sponsor
  - Informed Consent
  - Clinical Trial Protocol and Protocol Amendments
  - Investigator’s Brochure
  - Essential Documents for Conduct of a Clinical Trial
GCP Regulatory Requirements

- **Goals:**
  - Protect rights, safety and welfare of human research participants
  - Assure quality and integrity in data – reliability and reproducibility
  - Consistent standards to conduct the clinical research

- **Active Monitoring**
  - IRB Review
  - Sponsor/Investigator Quality Assurance Ongoing
  - FDA Audits Data at time of FDA Data Submission/Review
  - FDA For Cause Reviews
  - FDA Routine Reviews of IRB
Good Manufacturing Practices (GMP)

- GMP for drugs

Pharmaceutical Quality Resources

- CDER's Quality Initiative & the Office of Pharmaceutical Quality
- Quality Information for Applicants: Chemistry and Manufacturing Controls (NDA, BLA, IND, etc.)
- Quality Information for Manufacturers: Current Good Manufacturing Practices
- Advancing Product Quality
- FDA Presentations on Pharmaceutical Quality Topics
Good Manufacturing Practices (GMP)

- GMP for biologics

Vaccines, Blood & Biologics

CMC and GMP Guidances
Good Manufacturing Practices (GMP)

- GMP for devices

Quality System (QS) Regulation/Medical Device Good Manufacturing Practices

- Introduction
- Flexibility of the QS Regulation
- Applicability of the QS Regulation
- GMP Exemptions
- Additional Quality System Information
- Quality System Regulation and Preamble
Good Manufacturing Practices (GMP)

- Usually denoted as cGMP – current Good Manufacturing Practices
- Systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
  - To assure the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.
  - Quality management systems - appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.
  - Formal system of control to prevent instances of contamination, mix-ups, deviations, failures, and errors.
- Objective: assure that drug products meets quality standards.
Good Manufacturing Practices (GMP)

- FDA Regulatory Requirements:
  - cGMP in Manufacturing Processing, Packing or Holding of Drugs (21 CFR Part 210)
  - cGMP for Finished Pharmaceuticals Processing, Packing or Holding of Drugs (21 CFR Part 211)
  - cGMP for Positron Emission Tomography Drugs (21 CFR Part 212)

- cGMP address the minimum requirements for the methods, facilities and controls used in manufacturing, processing, packing, or holding of a drug product approved/regulated by FDA.
cGMP Regulatory Requirements

- Key Areas:
  - Organization and Personnel
  - Buildings and Facilities
  - Equipment
  - Control of Components and Drug Product Containers and Closures
  - Production and Process Controls
  - Packaging and Labeling Control
  - Holding and Distribution
  - Records and Reports
  - Returned and Salvaged Drug Products
cGMP Regulatory Requirements

- **Goal:** Consistent manufacturing and controls to quality standards for all aspects (product/article, labeling, packaging, holding)
  - Batch consistency (including batch identification)
  - Fitness for specified purpose
  - Safe and effective

- **Active Monitoring**
  - FDA Inspections prior to work beginning
  - Organization Quality Assurance ongoing (across process and across batches)
  - FDA Inspections routinely
Differentiation

GLP  <->  GMP

Test Facility Management  
QA  
Pharmaceutical Manufacturer

Archivist

Study Director

Analysis of Test item and “Specimen”

Approved Study Plan  
Master Schedule  
Final Report(s)

Feed Mixtures  
Animal Care  
Histology  
Bioanalytics

QA - Statement  
Study Audits  
Facility Audits

Batch Release  
BRR  
Self Inspection

Control of Raw materials and Products

Identity  
Purity  
Content  
CU  
Stability

Production, Packaging, Storage

Test Instruction  
Test Record  
Specifications  
Change Control  
OOS  
Complaints  
Recalls

Qualified Person

UT Southwestern Medical Center

Source: RAPS 2005 Annual Meeting
Transitioning to human testing

First regulatory milestone.

What is an investigational drug application?
Parallel activities that are critical to successful development

What is an “IND”? 

An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.
IND: First regulatory milestone

- Application submitted to the FDA to request approval to allow the use of a drug in humans to determine therapeutic potential.

  • The molecule changes in status to be a drug under the FD&C Act and is subject to the corresponding laws and regulatory system

  • The drug is subjected to an approval process before it can be transported across state lines

  • "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

  • Drug has been screened in animals for signals of pharmacologic action and indicators of toxicity; dosing strategy; adequate manufacturing quality.
IND: A Request to Start Clinical Trials

- Commercial IND - pharmaceutical companies whose ultimate goal is to obtain marketing approval for new products
- Investigator IND (Research IND) – submitted by physicians who initiates and conducts an investigation
- Single-Patient IND – a submission that is meant to treat only one patient
Examples

- **DRUGS: IND 117839**
  - Novel Therapies in Severe Acute Alcoholic Hepatitis: Efficacy of Anakinra, Pentoxyfylline and Zinc Sulfate Compared to Methylprednisolone

- **DEVICES: IDE G170127**
  - Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST – MST)

- **COMBINATION DRUG + DEVICE: IND 129123**
  - Liposomal Doxorubicin (Doxil®) Administered with MR-HIFU Hyperthermia for Relapsed and Refractory Solid Tumors
Role of the FDA in Drug Development

- Why is there oversight of drug development?
  - Legislation begets Regulations

- Why does the FDA get involved in drug development?
  - FDA mission:
    "FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable …"

- When does the FDA get involved?
FDA & Sponsor interactions during product development. Developers meet with the agency before submitting an IND, during clinical testing, methods of evaluation, and manufacturing issues.

What information is submitted to the FDA to allow human studies?

CTD data structure

Initial FDA submissions (INDs)
Sec. 312.23 IND content

1. Table of Contents
2. Introductory Statement and General Investigational Plan
3. Chemistry, Manufacturing, and Control Information
4. Pharmacology Toxicology Information
5. Investigator’s Brochure
6. Clinical Protocol(s)
7. Summary of Previous Human Experience with the Investigational New Drug
8. Additional Information, if applicable (e.g. drug dependence and abuse potential, pediatric studies, etc.)
9. Other Relevant Information, if applicable or if requested by FDA
IND Review

- 21 CFR 312.22

FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects and in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety.
IND Review

- 30-day review clock
  - Respond to any questions, information requests, or amendments from reviewer in timeframe

- Clinical hold
  - Safety concerns (known risk, inadequate information, Investigator’s Brochure misleading, Investigator not qualified)
  - Design will not allow protocol objectives to be met
  - Requires conference(s) with sponsor and division director with specific communication about what is required to lift the hold
FDA IND Review Team
## Characterization of Types of Expanded Access INDs

<table>
<thead>
<tr>
<th>Type of extended access (EA) IND</th>
<th>21 CFR 312.300</th>
<th>Number of patients</th>
<th>FDA review time</th>
<th>IRB approval</th>
<th>FDA approval</th>
<th>Course of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single patient-IND/protocol amendment</td>
<td>Nonemergency use §312.310</td>
<td>1</td>
<td>30 days</td>
<td>Approval needed prior to treatment</td>
<td>Approval needed prior to treatment</td>
<td>Usually 1</td>
</tr>
<tr>
<td></td>
<td>Emergency use §312.310(d)</td>
<td>1</td>
<td>Urgent</td>
<td>Report within 5 days</td>
<td>Approval prior to treatment; report within 15 days</td>
<td>Usually 1</td>
</tr>
<tr>
<td>Intermediate size patient population IND/protocol amendment</td>
<td>N/A §312.315</td>
<td>Smaller than typical Treatment IND (usually &lt; 100)</td>
<td>30 days</td>
<td>Approval needed prior to treatment</td>
<td>Approval needed prior to treatment</td>
<td>Defined in protocol</td>
</tr>
<tr>
<td>Treatment IND/protocol amendment</td>
<td>N/A §312.320</td>
<td>Written into protocol</td>
<td>30 days</td>
<td>Prereported</td>
<td>Prereported</td>
<td>Defined in protocol</td>
</tr>
</tbody>
</table>

Notes: Under the FDA’s EA program, there are several regulatory strategies available and the best one to use will depend on the particular factors for each situation. This table lists some of the key factors to consider when choosing which strategy to employ. In each of the four types of EA pathways, the use of protocol amendment submitted to an existing IND is the most straightforward and entails the least regulatory submission burden.

Exploratory IND: Phase 0

- Intended to expedite the clinical evaluation of new molecular entities
- Supports first-in-human (FIH) testing at subtherapeutic doses based on reduced manufacturing and toxicologic requirements
- Earliest demonstration of drug-target effects and assessment of pharmacokinetic-pharmacodynamic relationships in humans before larger numbers of subjects exposed
FDA & Sponsor interactions

Phase 1 studies

- The first few people in the study often get a very low dose of the treatment and are watched very closely. Dose escalation continues until doctors find a dose that’s most likely to work while having an acceptable level of side effects.

- Because of the small numbers of people in phase I studies, rare side effects may not be seen until later.

- Placebos (sham or inactive treatments) are not part of phase I trials.

- Overall, phase I trials are the ones with the most potential risk. But phase I studies do help some patients. For those with life-threatening illnesses, weighing the potential risks and benefits carefully is key.
Types of studies — Phase 1

Phase 1

- First-in-human Safety (e.g., dose escalation) studies
- Absorption, distribution, metabolism and/or excretion (ADME)
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Mass balance
- Dose proportionality
- Bioavailability (BA)
  - E.g. absolute or relative BA, formulation or dosage form changes or different routes of administration
- Bioequivalence studies (BE)
  - E.g., for manufacturing or formulation changes
- Food effects (fasting vs. fed)
- Drug-drug interactions
- Pharmacokinetics and/or Pharmacodynamics for specific populations
End of Phase 1 (EOP1)

Goal at the end of Phase 1 studies is to:

• Finalize formulation (dosage form) and route of administration (sometimes revised after Phase 2)
• Estimate the maximum tolerated dose (MTD)
• Establish maximum feasible dose
  – Example – number of times dosing required
  – Example – too much liquid to drink
• Establish safety profile in humans and based on animal toxicology studies
• Propose dosing regimen for Phase 2 studies
Phase 2 studies

**Purpose:** Test the efficacy of a drug or device.

- Can last from several months to two years, and involves up to several hundred patients.
- Most phase 2 studies are randomized trials; "control" receives a standard treatment or placebo.
- Often blinded
- About one-third of experimental drugs successfully complete both Phase 1 and Phase 2 studies.
Types of studies — Phase 2

- Dose ranging
- Population PK and/or PD
- Exposure response
- Pharmacogenomics / Pharmacogenetics
- Thorough QTc Studies (QT prolongation)
  - Could be done at any time (Phase I, II, or III)
- Clinical Pharmacology studies
- Early efficacy study
End of Phase 2 (EOP2)

Goal at the end of Phase 2 studies is to:

- Establish efficacy profile of drug in the diseased patient population
- Identify target patient population for seeking indication
- Establish dose-response (minimum effective dose, and optimal dose)
- Assess “short-term” safety
- Validate efficacy endpoints and duration of treatment
- Define dose or doses to go forward with in Phase 3
Phase 3 studies

Purpose: Efficacy and monitoring of adverse reactions

- Designed to demonstrate whether or not there is a treatment benefit to a specific population.
- Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants.
- Provide most of the safety data used in labeling.
Types of studies — Phase 3

Phase 3

- Usually 2 or more adequate and well-controlled trials (confirmatory studies)
  - Adequate—statistically powered studies with hundreds to thousands of patients with disease
  - Well-controlled—either placebo-control, or active-control, or multiple doses as controls Randomized and double-blind
  - Randomized, double-blind, multi-center, sometimes multi-national

- Population optimally heterogeneous
  - Approximately 25-30% of drugs move to the next phase
End of Phase 3 (EOP3)

Goal at the end of Phase 3 studies is to:

- Confirm the efficacy and safety of the new drug at the “to be marketed” dose, dosage form and mode of administration in the diseased patient population
- Confirm safety in large numbers
- Establish duration of treatment
- File a New Drug Application (NDA) with the FDA
Other Phases of Clinical Trials

- **Phase 4** - Post Approval (sometimes referred to as “post-marketing”)
  - Study Participants: Several thousand volunteers who have the disease/condition
  - Purpose: Safety and efficacy

- **Pragmatic Trials**
  - Approaches Clinical Research differently than randomized clinical trials
  - Designed with input from health systems (EMR), health providers, health providers and patients as “partners”
  - Intent is to accelerate research by integration of policy and practice
Exceptional Paths to Approval

- Expedited Programs for Serious Conditions
  - Fast Track
  - Breakthrough Therapy
  - Accelerated Approval

- Orphan Drugs
Non-Traditional Review Paths

- **Fast Track**: Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

- **Breakthrough Therapy**: A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.

- **Accelerated Approval**: These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.

- **Priority Review**: A Priority Review designation means FDA’s goal is to take action on an application within 6 months.

- **Orphan Drug**: A drug with a very small market granted special patent and approval considerations.
## Non-standard tracks

<table>
<thead>
<tr>
<th>Nature of program</th>
<th>Qualifying criteria</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast Track</strong></td>
<td>Designation</td>
<td>More frequent meetings with FDA; more frequent written communication from FDA Rolling review</td>
</tr>
<tr>
<td></td>
<td>potential to address unmet medical need OR a qualified infectious disease product</td>
<td></td>
</tr>
<tr>
<td><strong>Breakthrough Therapy</strong></td>
<td>Designation</td>
<td>More frequent meetings with FDA; more frequent written communication from FDA Rolling review Intensive guidance on drug development program Involvement of FDA senior managers to expedite development</td>
</tr>
<tr>
<td></td>
<td>demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
<td></td>
</tr>
<tr>
<td><strong>Accelerated Approval</strong></td>
<td>Approval Pathway</td>
<td>Approval based on a surrogate or intermediate endpoint (possible shorter development time) Note: FDA requires clinical trials to be conducted post-approval to confirm clinical benefit</td>
</tr>
<tr>
<td></td>
<td>meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit</td>
<td></td>
</tr>
<tr>
<td><strong>Priority Review</strong></td>
<td>Designation</td>
<td>Review of application in 6 months</td>
</tr>
<tr>
<td></td>
<td>significant improvement in safety or effectiveness OR submitted with a priority review voucher</td>
<td></td>
</tr>
</tbody>
</table>
Types of Review

Timeline for Drug Evaluation
<table>
<thead>
<tr>
<th>Approval Year</th>
<th>Drug (Brand Name)</th>
<th>Initial Indication</th>
<th>Surrogate Measure Used</th>
<th>Current Cost ($/mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Crizotinib (Xalkori)</td>
<td>Anaplastic lymphoma kinase (ALK)–positive locally advanced or metastatic non–small-cell lung cancer</td>
<td>Overall response rate based on Response Evaluation Criteria in Solid Tumors</td>
<td>14,353</td>
</tr>
<tr>
<td>2012</td>
<td>Bedaquiline (Sirturo)</td>
<td>In combination therapy for pulmonary multidrug-resistant tuberculosis</td>
<td>Time to sputum culture conversion</td>
<td>6,000</td>
</tr>
<tr>
<td>2013</td>
<td>Pomalidomide (Pomalyst)</td>
<td>Multiple myeloma that has progressed despite receipt of two prior therapies</td>
<td>Overall response rate, based on European Group for Blood and Marrow Transplant criteria</td>
<td>14,165</td>
</tr>
<tr>
<td>2014</td>
<td>Blinatumomab (Blincyto)</td>
<td>Philadelphia chromosome-negative relapsed or refractory B-cell acute lymphoblastic leukemia</td>
<td>Complete remission or complete remission with partial hematologic recovery rate</td>
<td>56,262</td>
</tr>
<tr>
<td>2014</td>
<td>Pembrolizumab (Keytruda)</td>
<td>Unresectable or metastatic melanoma with disease progression</td>
<td>Overall response rate based on Response Evaluation Criteria in Solid Tumors</td>
<td>9,252</td>
</tr>
<tr>
<td>2014</td>
<td>Ceritinib (Zykadia)</td>
<td>ALK-positive locally advanced or metastatic non–small-cell lung cancer with disease progression or intolerance to crizotinib</td>
<td>Overall response rate based on Response Evaluation Criteria in Solid Tumors</td>
<td>14,628</td>
</tr>
<tr>
<td>2015</td>
<td>Panobinostat (Farydak)</td>
<td>Multiple myeloma that has progressed despite receipt of two prior therapies</td>
<td>Progression-free survival based on European Group for Blood and Marrow Transplant criteria</td>
<td>10,625</td>
</tr>
<tr>
<td>2015</td>
<td>Palbociclib (Ibrance)</td>
<td>Postmenopausal women with metastatic estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer</td>
<td>Progression-free survival based on Response Evaluation Criteria in Solid Tumors</td>
<td>11,224</td>
</tr>
<tr>
<td>2016</td>
<td>Eteplirsen (Exondys 51)</td>
<td>Duchenne's muscular dystrophy in patients with confirmed mutation amenable to exon 51 skipping</td>
<td>Increase in dystrophin in skeletal muscle</td>
<td>57,600</td>
</tr>
</tbody>
</table>

* Initial indications and surrogate measures were obtained from drug labeling (www.accessdata.fda.gov/scripts/cder/daf/index.cfm). Costs of drugs were obtained from DrugAbacus (run by the Memorial Sloan Kettering Cancer Center) in November 2016, except for the cost of bedaquiline, which is based on the average wholesale price (AWP) of $36,000 for 24 weeks of treatment (as reported in UpToDate), and the cost of eteplirsen, which is based on the AWP of $1,920 per 100 mg (assuming a patient weighing 25 kg and a dose of 30 mg per kilogram of body weight once weekly), or $691,000 per year. Publicly reported estimates of $300,000 included presumed discounts.
Parallel activities that are critical to successful development

Basic Research  Prototype Design or Discovery  Preclinical Development  Clinical Development  FDA Filing/Approval & Launch Preparation

Safety  Prototype Design or Discovery  In vitro and animal testing  Human and animal testing  Safety follow-up

Medical utility  In vitro and Computer model evaluation  In vitro and animal models  Human efficacy evaluation

Industrialization  Physical design  Characterization and small scale production  Manufacturing scale-up Refined specifications  Mass production

Basis for NDA approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies

- Ability to generate product labeling that
  - Defines an appropriate patient population for treatment with the drug
  - Provides adequate information to enable safe and effective use of the drug
NDA Types

Type 1: New Molecular Entity (NME)
Type 2: New Active Ingredient (e.g. new salt)
Type 3: New Dosage Form
Type 4: New Combination
Type 5: New Formulation or New Manufacturer
Type 6: New Indication, Same Manufacturer (no longer used)
Type 7: Drug Already Marketed, but Without Approved NDA
Type 8: Rx to OTC
NDA components

- Index
- Proposed labeling
- Application Summary
- Pharmaceutical quality, chemistry, manufacturing, and controls
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Clinical microbiology
- Clinical data
- Safety data
- Statistics
- Case reports tabulations
- CRFs
- Patent information
- Patent certification
- Establishment certification
- Debarment certificate
- Field copy certificate
- User fee certificate
- Financial disclosure
Industry & FDA interactions during product development. Developers meet with the agency before submitting an IND, during clinical testing, methods of evaluation, and manufacturing issues.

FDA NDA Review Team

- Medical Officer
- Clinical Pharmacology/Biopharmaceutics
- Chemists/Biologists/Microbiologists
- Project Manager
- Statistician
- Pharmacology/Toxicology
FDA approves a drug with any or all of the following specifications as spelled out in the Official Product Labeling:

- Chemical entity
- For specific medical conditions
- Specific populations
- Dose/duration
- Form of the drug (e.g. capsule vs. tablet)
- Route of administration
- With accompanying warnings and contraindications

Any use outside of labeling MAY require approval.
Biologics

- Biological Product - “A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings”

- Therapeutic biological products were transferred from CBER to CDER in 2003
Therapeutic Biologic Products

- Monoclonal antibodies of in vivo use
- Proteins intended for therapeutic use that are extracted from plants, animals or microorganisms, including recombinant versions
- Cytokines, growth factors, enzymes, immunomodulators and thrombolytics
- Other non-vaccine therapeutic immunotherapies
Basis for BLA approval

- License granted for products that meet standards designed to insure “continued safety, purity, and potency” of the product
- “Potency” interpreted as “efficacy”

Ref: 42 U.S. Code section 262 – Regulation of biological products
21 CFR 600.3(s)
What about devices?
Device approval process

1. Determine if you have a device by FDA definitions
2. Determine device classification
3. Choose correct premarket submission
4. Prepare information for FDA
5. Send Premarket Submission to FDA (and interact with review)
6. Complete Establishment Registration and Device Listing
7. Design control provisions of the Quality System Regulation (QRS)
Is it a device?

Definition:

• A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

- Refer to FDA CDRH database to look for similar product.

- Even if your medical device does not require a premarket submission, be sure to have the correct classification.
Does it emit radiation?

- Ionizing electromagnetic radiation
- Particulate radiation and ionizing electromagnetic radiation
- Ultraviolet
- Visible
- Infrared
- Microwave
- Radio and low frequency
- Laser
- Maser
- Infrasonic
- Sonic
- Ultrasonic

1. Certain radiation emitting products require the submission of product reports to FDA and the retention of records as included in 21 CFR Part 1002.

2. All manufacturers of electronic products are subject to the reporting of accidental radiation occurrences, as required by 21 CFR 1002.20.
Is it a combination product?

- A medical device plus another FDA-regulated product (e.g. drug, biologics, etc.)
- Based on your product’s primary mode of action, Office of Combination Products will tell you which FDA Center that you need to contact in order to market the product.
Medical Device Classification

- Devices are classified according to the risk associated with use of the device:
  - Class I; lowest risk
  - Class II; moderate risk
  - Class III; highest risk
Unlike drugs: oversight and regulations are stratified.
Overview of Device Classification

Product a CDRH device?

- Yes
  - Is there a similar device?
    - Yes
      - Class I (General Controls)
    - No
      - Class II (General Controls + Special Controls)
- No
  - No, Automatic Class III
    - Class III (General Controls + PMA)
      - PMA Application
      - Alternate Pathways
        - De Novo Request
        - HDE Submission
      - CDER, CBER
Pathways for marketing medical devices in US
Pathways for marketing medical devices in US
Pathways for marketing medical devices in US
CONTROLS Designations

- **General Controls** – The means by which the FDA regulates the safety and efficacy of devices

- Pertain to:
  - Adulteration;
  - Misbranding;
  - Device registration and listing;
  - Premarket notification;
  - Banned devices;
  - Notification and repair, replacement, and refund;
  - Records and reports;
  - Restricted devices; and
  - Good Manufacturing Practices.
**CONTROLS Designations**

- **Special Controls** — regulatory requirements for Class II devices.
  - General controls insufficient to provide reasonable assurance of safety and effectiveness

- Device-specific and include:
  - Performance standards
  - Postmarket surveillance
  - Patient registries
  - Special labeling requirements
  - Premarket data requirements
  - Guidelines
CONTROLS Designations

- Premarket Approval (PMA)
  - Class III devices
Repurposing an FDA approved device for research IDE

Commercialization Options

**Exempt** of the premarket notification requirements (510(k)).
- most Class I and a few Class II devices are exempt

**510(k)** – Marketing notification that demonstrates the new device is at least as safe and effective, or substantially equivalent to, a legally marketed device that is not subjected to a PMA.
- 90 day FDA review http://tinyurl.com/qeh79qn

**PMA** – Premarket approval application that is required for all Class III devices. Focus on scientific and regulatory review of safety and effectiveness.
- 180 day FDA review
Types of 510(k) Submissions?

- Traditional 510(k)
- Abbreviated 510(k)
- Special 510(k)
Premarket Approval (PMA)

- Scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

- Independent assessment of safety and effectiveness.
  - Approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).

- Devices found not substantially equivalent (NSE) in a 510(k) application may need to submit a PMA before marketing.
Premarket Approval (PMA)

Two Technical Sections:

- Non-clinical Laboratory Studies' Section:
  - Includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests.
  - Non-clinical studies for safety evaluation must be conducted in compliance with GLP.

- Clinical Investigations' Section:
  - Includes all information from clinical studies, including protocols, safety and effectiveness data, adverse reactions, device failures, statistical analyses, etc.
  - Any investigation conducted under an Investigational Device Exemption (IDE) must be identified as such.
Humanitarian Use Device (HUD)

- Humanitarian Use Device = a device treating a disease affecting <4,000 in the US per year (incidence)
- A HUD then undergoes further FDA/CDRH review to determine if it qualifies for a Humanitarian Device Exemption (HDE)
Humanitarian Device Exemptions (HDE)

- HDE is similar to a pre-market approval (PMA) but is exempt from the effectiveness requirement.

BUT, must be

- Not for profit (unless pediatric device)
- Device has to be used with IRB approval
- No comparable device marketed

- FDA/CDRH approval of a HDE authorizes marketing of the HUD
What about apps?

Mobile Medical Applications (MMA)

Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff (02/09/15; doc. 1741).
www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm
What are mobile medical apps (MMA)?

Mobile Medical Application (Mobile Medical App)

- a “mobile medical app” is a mobile app that meets the definition of device in section 201(h) of the FD&C Act 4; and either is intended:
  - to be used as an accessory to a regulated medical device; or
  - to transform a mobile platform into a regulated medical device.
What are mobile medical apps (MMA)?

- Software programs that run on smartphones and other mobile communication devices.
- Also accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software.
Who uses mobile medical apps?

- Consumers
  - Can use both mobile medical apps and mobile apps to manage their own health and wellness, such as to monitor their caloric intake for healthy weight maintenance.
  - For example, the National Institutes of Health’s LactMed app provides nursing mothers with information about the effects of medicines on breast milk and nursing infants.

- Health care professionals
  - Can improve and facilitate patient care.
  - The Radiation Emergency Medical Management (REMM) app gives health care providers guidance on diagnosing and treating radiation injuries.
  - Some mobile medical apps can diagnose cancer or heart rhythm abnormalities, or function as the “central command” for a glucose meter used by an insulin-dependent diabetic patient.
How will the FDA regulate mobile medical apps?

- The FDA will apply the same risk-based approach the agency uses to assure safety and effectiveness for other medical devices.

- Developers should contact the FDA if they have any questions about their mobile app, its level of risk, and whether a premarket application is required.

- The 21st Century Cures Act (12/13/2016) amended the definition of “device” in the Food, Drug and Cosmetic Act to exclude certain software functions.
Mobile medical apps that the FDA will regulate:

- FDA will take a tailored, risk-based approach that focuses on the small subset of mobile apps that meet the regulatory definition of "device" and that:
  - are intended to be used as an accessory to a regulated medical device, or
  - transform a mobile platform into a regulated medical device.
- Many mobile apps carry minimal risk; those that can pose a greater risk to patients will require FDA review.
- FDA’s mobile medical apps policy does not require mobile medical app developers to seek Agency re-evaluation for minor, iterative product changes.