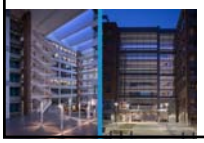
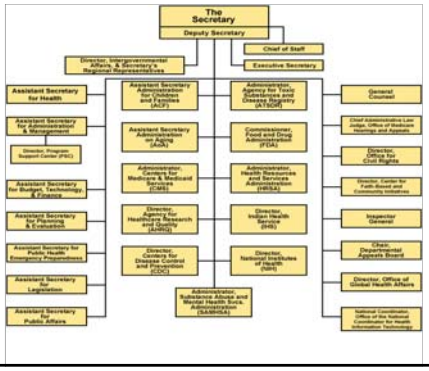
The Regulation of Drug and Biological Products

Introduction to the Principles and Practice of Clinical Research



FDA White Oak Campus

Where is the FDA -DHHS



Food and Drug Administration

Commissioner:

Margaret A. Hamburg , M.D.

Food and Drug Administration



- Center for Veterinary Medicine
- Center for Food Safety and Applied Nutrition
- National Center for Toxicological Research
- Office of Regulatory Affairs
- Center for Tobacco Products

Mission of the FDA

- 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.
- FDA is 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.
- FDA has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
- Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Food and Drug Administration

- Center for Biologics Evaluation and Research
- Center for Drug Evaluation and Research
- Center for Devices and Radiological Health

Tragedies lead to Legislative and Regulatory Actions

Tragedy	Legislation
• 14 children die of tetanus in 1901 from contaminated horse serum ("Jim")	• Biologics Control Act of 1902
• Cure-all claims for worthless and dangerous patent medicines	• Food and Drug Act of 1906
• 100 die due to diethylene glycol in elixir of sulfanilamide in 1936	• Federal FD&C Act of 1938
• "Cutter incident"; 260 children contract polio and/or die in 1955 from Salk vaccine which was not properly inactivated	• Division of Biological Standards Created within NIH

Tragedies lead to Legislative and Regulatory Actions

Tragedy	Legislation
• Thalidomide, sleeping pill, causes severe birth defects in thousands of babies in western Europe in 1962	• Kefauver-Harris Drug Amendments of 1962
• Cyanide poisoning via Tylenol capsules in 1982	• Federal Anti-Tampering Act of 1983

Statutory and Regulatory Authorities

Pharmaceutical Product	Food Drug & Cosmetic Act	Public Health Service Act	Interstate Commerce	Foreign Commerce	Component Jurisdiction	Generic Equivalence	Good Manufacturing Practices	PDUFA*	FDA MA 1997
Drug	✓		✓		✓	✓	✓	✓	✓
Biologic	✓	✓	✓	✓	✓		✓	✓	✓

* Prescription Drug User Fee Act

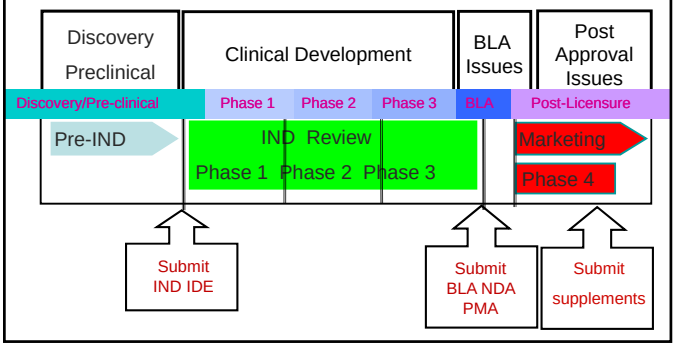
Biologics Price Competition and Innovation 2010

- Part of the PPAC Act signed by President Obama in March 2010
- Adds an approval pathway for biosimilar biological products
- Redefines biological products to include "protein, except any chemically synthesized polypeptide"
  - Unless otherwise meets the definition of a biologic
- Adds exclusivity protection

Food and Drug Administration Science and Innovation Act (FDASIA) 2012

- Reauthorized User Fees
  - Drugs & Biologics (PDUFA V)
  - Devices (MDUFA III)
- Instituted User Fees
  - Generic Drugs (GDUFA I)
  - Biosimilars (BSUFA I)
- Created
  - Breakthrough Therapy Designation
  - Drug Supply Security

Drug & Biologic Product Lifecycle



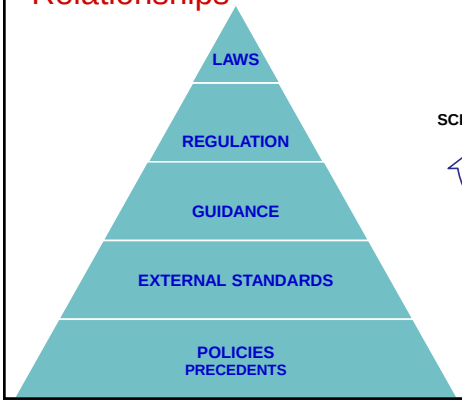
Regulations for Medical Products
Title 21, Code of Federal Regulations (CFR)

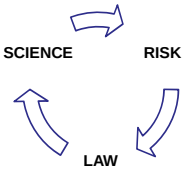
- Part 201, 202 - Labeling & Advertising
- Part 312 - Investigational New Drug (IND) and Part 314 - New Drug Application (NDA)
- Parts 600 - 680 Biologics [Public Health Service Act] (BLA)
- Part 800 - 861 Devices & In Vitro Diagnostics

Regulations for Medical Products
Title 21,Code of Federal Regulations (CFR)

- Part 25 - Environmental Impact Considerations
- Part 50 - Protection of Human Subjects
- Part 54 - Financial Disclosure by Clinical Investigators
- Part 56 - Institutional Review Boards
- Part 58 - Good Laboratory Practices for Non-Clinical Laboratory Studies

Relationships





Guidance Documents

- Developed with input from many sectors: academia, other government components, industry, public fora, e.g., workshops, meetings, ICH
- Good Guidance Practices
- Flexible and allow for case-by-case assessment
- Example: **Guidance for Industry**

> **Guidance for Industry**
>
> Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies
>
> 9/10

Definition of IND

- ***IND** refers to* a drug or biological drug used in a clinical investigation.
- Does not apply to use of an approved product under "practice of medicine"
- An investigational new drug for which an *IND* application is in effect … **is exempt from the premarketing approval requirements … and may be shipped lawfully for the purpose of conducting clinical investigations of that drug. 21 CFR 312.1(a) from 505(i) of the FDCA**

21 CFR 312 Investigational New Drug Regs and Good Clinical Practice (GCP) Consolidated Guideline (ICH E6)

- GCP is a unified standard for designing, conducting, recording & reporting clinical trials.
- Content and Format of IND and the Investigator's Brochure (IB)

Both are essential reading for clinical trial design/performance & data evaluation.

Investigational New Drug Application 21CFR 312 Subpart B

- Applicability
- Phases of Investigation
- IND must be in effect (not “approved”) before clinical investigation can begin
- IND Content and Format (read guidance)
- Protocol and Information Amendments
- IND Safety Reports
- IND Annual Reports
- Withdrawal of an IND

Phases of a Clinical Investigation

- Phase I Studies
  - Small number of subjects, generally less than 50
  - 1ºFocus on safety (tolerability)
  - 2ºPreliminary evidence of activity
  - Dose escalation
- Phase II Studies
  - Generally up to a few hundred subjects
  - 1ºFocus on safety (tolerability)
  - 2º Demonstrate Activity
  - Dose esclation/ finding
  - Activity assessment

Phases of a Clinical Investigation

- Phase III Studies
  - Size is dependent on disease, population and study design
  - Confirm clinical benefit
  - Expand knowledge of safety
  - Evaluate the overall benefit-risk relationship for the product
  - Provide an adequate basis for labeling
  - Pivotal safety and efficacy studies, data form basis of marketing application

General Principles of the IND Submission [21 CFR 312.22]

- All Phases:
  - to assure the safety and rights of subjects
- Phase 2 & 3, in addition
  - 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

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Clinical Hold in Phase 1: Safety

Grounds for imposition of clinical hold in Phase 1:

- (i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury
- (ii) The clinical investigators are not qualified by reason of their scientific training and experience
- (iii) The investigator brochure is misleading, erroneous, or materially incomplete
- (iv) The IND does not contain sufficient information to assess the risks to subjects of the proposed studies.
- (v) Study for a life-threatening disease that affects both genders, and trial excludes based on gender

Clinical Hold in Phase 2 & 3: Safety and Trial Design

Grounds for imposition of clinical hold in Phase 2 & 3:

- (i) Any of the conditions applicable to Phase 1 Studies apply; or
- (ii) The plan or protocol for the investigation is **clearly deficient in design** to meet its stated objectives.

Quality and Safety Issues - Manufacturing Biological Products

- Raw materials and seed banks
- Production, e.g. fermentation, harvesting, purification, storage of the bulk, formulation, final fill
- Characterization
- Process validation
- Testing

Manufactured in compliance with cGMP

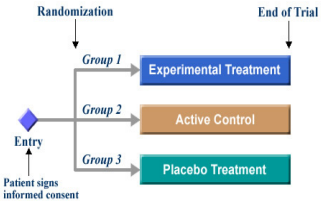
Phase 1 comply with FD&C Act, exempt from 211 regulations

Pharmacology and Toxicology Considerations

- Planned Clinical Evaluation
- Selection of Relevant Animal Model if existing
- Animal Pharmacokinetic
- Immunogenicity Data

Clinical Considerations

- Trial Design and Analysis
- Conduct and Monitoring of Trial
- Adverse Event Reporting
- Pediatric Development
- Demographic Subgroups



Principles of Good Clinical Practice ICH E6

- A clinical trial should be conducted in accordance with ethical principles which are consistent with GCP and applicable regulatory requirements
  - Initiated and continued only if the anticipated benefits justify the risks, with the individual trial subjects' safety prevailing over the interests of science and society
  - Supported with adequate clinical and non-clinical investigational product information
  - Described in a clear, detailed protocol which is scientifically sound

Principles of Good Clinical Practice (2)

- Conducted in compliance with the protocol which has prior IRB/IEC approval
- Conducted by qualified individuals with only qualified physicians responsible for medical decisions made on behalf of the subjects
- Initiated only after obtaining informed consent from each subject prior to enrollment
- Data protected from invalidation by proper recording, handling and storage of trial information allowing accurate reporting, interpretation and verification

Principles of Good Clinical Practice (3)

- Conducted in accordance with the regulatory requirements on confidentiality of records which protect subjects' identity
- Conducted using investigational products manufactured, handled and stored in accordance with GMPs and the approved protocol
- Systemized with procedures that assure the quality of every aspect of the trial

Investigator's Responsibilities

- Conducting clinical trial at his/her site
- Adhering to investigational plan and regs
- Human subject protection
- Assurance of IRB review
- Obtaining informed consent
- Case histories – case report forms, etc.
- Record retention – at least 2 years

Investigator's Responsibilities (2)

- Control and disposition of investigational product
- REPORTS to SPONSOR
  - Progress reports
  - Safety reports
  - Final reports
  - Financial disclosure reports

Sponsor Responsibilities

- Investigator/institution selection
- Provide Investigators Brochure to all PIs before study begins
- Notification/submission of application to regulatory authorities
- Ensure that investigation is being conducted according to plan
- Promptly inform PIs and FDA of significant new adverse effects or risks of drug
- Adequate monitoring
- Interactions with FDA
- Act on investigator non-compliance
- Notification of premature termination or suspension
- Study reports

Sponsor Responsibilities (2)

- Keep PIs informed of new observations, particularly regarding safety via IB, reprints, etc.
- Adverse Event Reporting
- Quality Assurance/Quality Control, Standard Operating Procedures
- Trial and data management
- Allocation of duties and functions – i.e. CRO
- Auditing
- Investigational product

Sponsor Responsibilities (3)

FDA Amendments Act of 2007

- Requires expansion of NIH clinical trials registry
  - All controlled clinical trials other than phase I
  - Made easily searchable for the public on a variety of elements
  - Includes trial results link for pivotal trials
  - ClinicalTrials.gov: http://www.clinicaltrials.gov
- Include Certification Form with every submission to FDA
  - http://www.fda.gov/cder/regulatory/FDAAA_certification.htm
  - http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf

Sponsor Responsibilities (4)

- Monitoring
  - –to verify that rights and well-being of human subjects are protected
  - –reported data are accurate, complete, verifiable
  - –compliance with protocol, GCP, regulations
- Sponsor must select qualified monitors and train appropriately

Safety Review During IND:
IND Safety Reports [21 CFR 312.32]

The sponsor must notify FDA and all participating investigators:

Within **15** days in writing or:

- Serious and unexpected suspected adverse reactions
- Findings from other studies or from *in vitro* or animal testing that suggest a significant risk for humans (including reports of mutagenicity, teratogenicity, or carcinogenicity
- Increased rate of serious suspected adverse reactions over that listed in protocol or investigator brochure

As soon as possible but within **7** days by telephone or fax for:

- Unexpected fatal or life-threatening suspected adverse reactions

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Safety Review During IND:
IND Safety Reports [21 CFR 312.32]

Definition:

Suspected Adverse Reaction

"Any adverse event for which there is a reasonable possibility that the drug caused the adverse event."

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Safety Review During IND
Annual Reports [21 CFR 312.33]

- Summary safety data from ongoing and completed clinical studies, including:
  - Number of subjects planned and enrolled, dropouts
  - Most frequent and most serious adverse experiences
  - Summary of IND safety reports submitted the past year
  - Deaths and causes
- A list of preclinical studies completed or in progress, with a summary of major findings
- A summary of significant manufacturing changes
- A description of the general investigational plan for coming year
- A copy of the investigator brochure if revised, with description of revisions
- Foreign marketing developments

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IND Safety Reporting Requirements

- Expedited Reports- Guidance September 2010 “Safety Reporting Requirements for INDs and BA/BE Studies”
- Annual Reports or Information Amendments

Protection of Human Subjects

21 CFR 56: Institutional review board (IRB)

Definition: Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.

Compliance with Part 56 is intended to protect the rights and welfare of human subjects involved in biomedical research.

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Institutional Review Board (21 CFR 56)

- Review and Approve All Protocols to Assure that:
  - Risks to subjects are minimized and reasonable
  - Selection of subjects is equitable
  - Informed consent will be sought and documented

Institutional Review Boards (IRB)
[21 CFR 56 & 50]

- Have at least five members, with varying backgrounds
- Review and have authority to approve, require modifications in, or disapprove all research activities at the institution
- Are responsible for the adequacy and documentation of **informed consent** in clinical trials
- Conduct continuing review of research at least once per year
- Must determine that the research is in compliance with **special protections for children [part 50]**
- Maintain records of IRB activities for at least **3 years** after completion of the research, and the records shall be accessible for inspection and copying by FDA

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Informed Consent: Required Elements
[21 CFR 50]

(1) Explanation of the purposes of the research, duration and procedures
(2) Description of reasonably foreseeable **risks** to the subject
(3) Description of **benefits** to the subject, if any
(4) Disclosure of alternative procedures or treatment, if any
(5) Description of the extent to which confidentiality will be maintained and notation that FDA may inspect and copy records
(6) Explanations regarding compensation, available medical treatments if injury occurs, and where additional information may be obtained
(7) Identification of contacts for answers to pertinent questions, and in the event of a research-related injury
(8) Statements that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits, participation may be discontinued at any time without penalty or loss of benefits

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Human Subjects Protections: Additional Safeguards for Children in Clinical Investigations [21 CFR 50 Subpart D]

- Clinical Research in Children is approvable if:
  - **50.51** Not more than minimal risk, or
  - **50.52** Prospect of direct benefit for the individual subject, or
  - **50.53** Likely to yield generalizable knowledge about the subjects' disorder or condition, or
  - **50.54** Not otherwise approvable, but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (Must be referred to FDA Commissioner for panel review)

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Pediatric Research Equity Act of 2007 / FDA Safety and Innovation Act of 2012

- Requires a manufacturer of a drug or biologic who submits an application to market a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration ***to submit a plan for assessment in pediatrics.***
- Pediatric plans contain summary of planned nonclinical and clinical studies, plans for any pediatric-specific formulation development, description of data needed to support initiation of pediatric studies, and timeline
- Goal is a pediatric plan that is adequate to assess safety and effectiveness, and to support dosing and administration, in the relevant pediatric subpopulations.
- Based on established criteria, FDA may
  - waive the requirement for a pediatric assessment for some or all age groups
  - defer the timing of submission of some or all of the pediatric assessment

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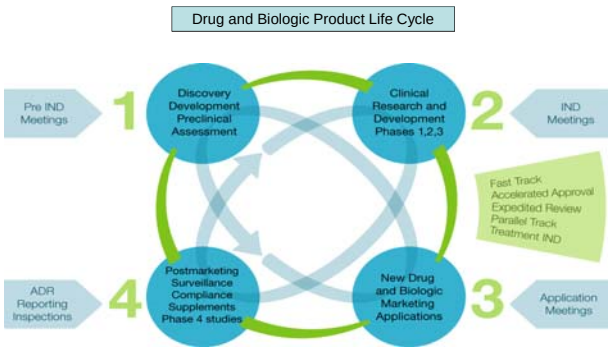
Bioresearch Monitoring

- To ensure the quality and integrity of data submitted to FDA in support of an IND / IDE or BLA / NDA / PMA / other application
- To ensure that the rights and welfare of the human research subjects are protected

21 CFR 312 Subpart H (2009)

- Expanded Access to INDs
  - Criteria
    - Serious/life threatening condition, and no satisfactory alternative
    - Potential benefit justifies risks
    - Won't interfere with ongoing clinical trials
  - Examples
    - Individual patients
    - Mid size populations
    - Treatment IND
  - Cost Recovery



Expedited Programs

- Four expedited programs
  - –Fast track designation (FT)
  - –Breakthrough therapy designation (BT)
  - –Accelerated approval (AA)
  - –Priority review designation (PR)

Fast Track Designation

- Criteria
  - – Serious condition, **and**
  - – Nonclinical or clinical data demonstrate the potential to address unmet medical need
- Features
  - – Actions to expedite development and review
  - – Rolling Review

Fast Track Designation

- Criteria
  - Serious condition, **AND**
  - Nonclinical or clinical data demonstrate the potential to address unmet medical need
    - NOTE: Information to demonstrate potential depends upon stage of development at which FT is requested
- Features
  - Actions to expedite development and review
    - PDUFA granted meeting plus other meetings as appropriate
  - Rolling Review

Breakthrough Therapy Designation

- Criteria
  - Serious condition **AND**
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints
- Features
  - All of FT features (i.e., expedited development and review, rolling)
  - Intensive guidance on efficient drug development
  - Organizational commitment
  - Other actions to expedite review – Priority Review

Accelerated Approval

- 21CFR 314.510 and 601.41
- FDA approval can be based on a surrogate endpoint that is reasonably likely to predict clinical benefit or clinical effects that are not the desired ultimate benefit but are reasonably likely to predict such benefit.

Priority Review of a MA

- A significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a severe and life-threatening illness
- Complete review of a marketing application within 6 months (90% goal)

Orphan Drugs
21CFR Part 316

- No current therapy exists or product will significantly improve the current therapy.
- **Orphan Designation** " … intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/ disorders that affect fewer than 200,000 people in the US, or effects more, but not expected to recover the costs of development and marketing a drug
- Exclusivity – 7 years, (unless fails to supply market demand,)
- Apply for grants, waiver of User Fees

Standards of Licensure

- Safety
- Purity
- Potency
- Stability
- Product Quality

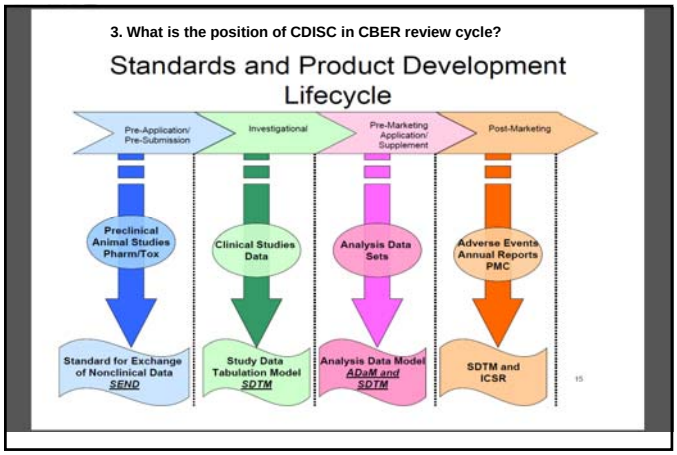
- cGMP Compliance

Post Marketing Surveillance and Compliance

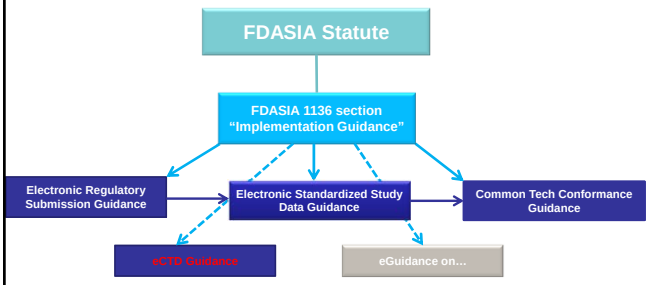
- Adverse Event Reporting
  (21CFR 600.80)
  15-Day “Alert Reports”
  (21CFR 314.80)
- Inspections
- Enforcement
- Education

Recent/ Up and Coming

- Adaptive Clinical Trial Design
- Biomarkers & “…omics”
- Demographic Subgroups
- Big Data
- Structured Data
- Combination Products



The FDA "*New* Current" Thinking



Resources for FDA

- **FDA's Home page : www.fda.gov**
- **Code of Federal Regulations: www.gpoaccess.gov/cfr/index.html or www.fda.gov**