The Regulation of Drug and Biological Products
Introduction to the Principles and Practice of Clinical Research

Photo: FDA White Oak Campus
FDA White Oak Campus
WHERE IS THE FDA? DHHS

Graphic:
Organizational chart
Food and Drug Administration

Commissioner:

Margaret A. Hamburg, M.D.
Photo of the Commissioner
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health

Graphics to represent the centers
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

Graphics to represent the centers
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.
Tragedies lead to Legislative and Regulatory Actions

Tragedy
14 children die of tetanus in 1901 from contaminated horse serum ("Jim")

Cure-all claims for worthless and dangerous patent medicines

100 die due to diethylene glycol in elixir of sulfanilamide in 1936

"Cutter incident"; 260 children contract polio and/or die in 1955 from Salk vaccine which was not properly inactivated

Legislation

Biologics Control Act of 1902

Food and Drug Act of 1906

Federal FD&C Act of 1938

Division of Biological Standards Created within NIH
Tragedies lead to Legislative and Regulatory Actions

Thalidomide, sleeping pill, causes severe birth defects in thousands of babies in western Europe in 1962

Cyanide poisoning via Tylenol capsules in 1982

Kefauver-Harris Drug Amendments of 1962

Federal Anti-Tampering Act of 1983
Statutory and Regulatory Authorities Graphic
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”
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 Drugs, Devices & Biological 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
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

Graphic
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 Protocol and Information Amendments
IND Safety Reports
IND Annual Reports
Withdrawal of an IND
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
Graphic: Drug and Biologic Product Life Cycle
Phases of a Clinical Investigation

Phase I Studies
- Small number of subjects, generally less than 50
- Focus on safety

Phase II Studies
- Generally up to a few hundred subjects
- Safety and dose selection
- Activity assessment

Phase III Studies
- Pivotal safety and efficacy studies, data form basis of marketing application
- Size is dependent on disease, population and study design

Graphic
Fast Track Drug Development Program
Criteria for Qualification
- Serious or Life-threatening Condition
- Potential to Address Unmet Medical Need
Process for Designation
Programs for Expediting Development and Review

Graphic
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.

Graphic
Priority Review of a MA
Center for Biologics Evaluation and Research
  A significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a severe and life-threatening illness
Center for Drug Evaluation and Research
  A significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease
  Complete review of a marketing application within 6 months (90% goal)
Clinical Hold (21 CFR 312.42)

IND Phase 1
Subjects exposed to an unreasonable and significant risk of illness or injury
Clinical investigator is not qualified
Investigator’s Brochure is misleading, erroneous or materially incomplete
IND does not contain sufficient information to assess risk
Women or men excluded to avoid potential for reproductive or developmental toxicity
• Clinical Hold

**IND** Phase 2 and 3

• All the Phase 1 reasons &/OR

• Protocol is clearly deficient in design to meet its stated objectives
Quality and Safety Issues Associated with 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
Pharmacology and Toxicology Considerations

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

Photo: White mouse
Clinical Considerations
Trial Design and Analysis

Conduct and Monitoring of Trial

Adverse Event Reporting

Graphic
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/FDA_AA_certification.htm
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
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
At least five members with varying backgrounds
IND Safety Reporting Requirements

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

Annual Reports or Information Amendments
Written Reports: §312.32 (c)
Any AE associated with use of the study drug that is both serious and unexpected
Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity
Sponsor to notify FDA and all participating investigators as soon as possible but no later than 15 calendar days after receipt of the information
Telephone/Facsimile Safety Reports §312.32 (c)  
“The sponsor shall also notify FDA by telephone or facsimile of any unexpected fatal or life threatening experience associated with use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor’s initial receipt of the information.”
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

Graphic: Detective
Standards of Licensure

Safety
Purity
Potency
Stability
cGMP Compliance
Post Marketing Surveillance and Compliance

Adverse Event Reporting
(21CFR 600.80)

15-Day “Alert Reports”
(21CFR 314.80)

Inspections

Enforcement

Education
Resources for FDA Documents

FDA’s Home page:  
www.fda.gov

ICH Guidance Documents:  
www.ich.org

Code of Federal Regulations:  
www.gpoaccess.gov/cfr/index.html or  
www.fda.gov
One More Resource…
REPUTATION AND POWER by Dr. Daniel Carpenter, political scientist

“Magisterial new history of the FDA” The New Yorker magazine
Argues that a key to FDA’s success has been its staffers’ dedication to protecting and enhancing its reputation for competence and vigilance.
This reputation has led to regulated companies’ willingness to respect its authority (in contrast to other government regulatory authorities).