FDA Structure and Mandate

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Clinical Investigator Training Course

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Learning Objectives

- Provide a brief history of FDA
- Describe the current mission of FDA
- Introduce FDA's legal and regulatory framework for drugs and biologics

Brief History of FDA

- Built on legacy of public health failures
  - Unsafe, ineffective, counterfeit, or adulterated drugs
  - Unethical practices and fraud

Copyright Museum of Health Care

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black

Brief History of FDA

1848: Drug Importation Act

1902: Biologics Control Act

1906: Pure Food and Drug Act

1912: Sherley Amendment

1938: Food, Drug, and Cosmetic Act

1944: Public Health Service Act

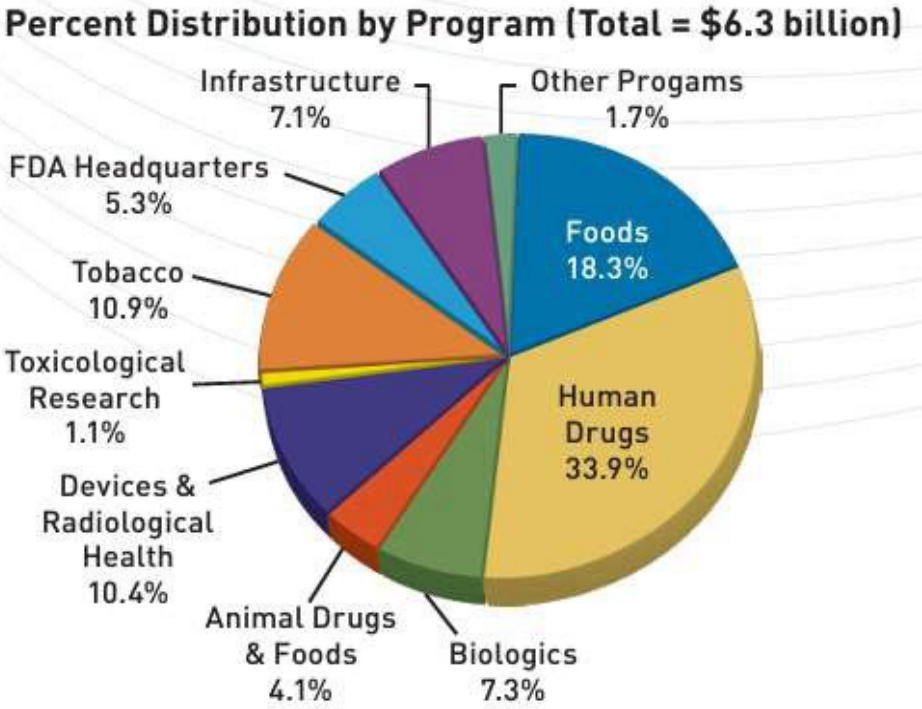
1951: Durham-Humphrey Amendment

1962: Kefauver-Harris Drug Amendments

1968: Drug Efficacy Study Implementation (DESI)

Overview of FDA

- ~18,650 employees
- Oversees safety of more than $3.6 trillion worth of food, tobacco, and medical products, accounting for 21 cents of every dollar spent by U.S. consumers



fda.gov/cdersbia

https://www.fda.gov/media/175664/download

Legal Framework: Statute

Federal Food, Drug, and Cosmetic Act (FD&C Act) & Public Health Service Act: provides statutory authority for FDA's oversight of clinical investigations to evaluate safety and effectiveness

Legal Framework: Regulations

Code of Federal Regulations (CFR): implement FDA's statutory authority over conduct of clinical investigations

Title 21 Food and Drugs		Part / Section
Chapter I	Food and Drug Administration, Department of Health and Human Services	1 – 1299
Subchapter A	General	1 – 99
Subchapter B	Food for Human Consumption	100 – 199
Subchapter C	Drugs: General	200 – 299
Subchapter D	Drugs for Human Use	300 – 499
Subchapter E	Animal Drugs, Feeds, and Related Products	500 – 599
Subchapter F	Biologics	600 – 680
Subchapter G	Cosmetics	700 – 799
Subchapter H	Medical Devices	800 – 898
Subchapter I	Mammography Quality Standards Act	900
Subchapter J	Radiological Health	1000 – 1040
Subchapter K	Tobacco Products	1100 – 1150
Subchapter L	Regulations Under Certain Other Acts Administered by the Food and Drug Administration	1210 – 1299

FDA Guidance

- Advisory, to assist regulated entities in complying with regulations and to understand FDA's current thinking on a topic


GUIDANCE DOCUMENT

Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices

Draft Guidance for Industry

SEPTEMBER 2021


GUIDANCE DOCUMENT

Informed Consent

Guidance for IRBs, Clinical Investigators, and Sponsors

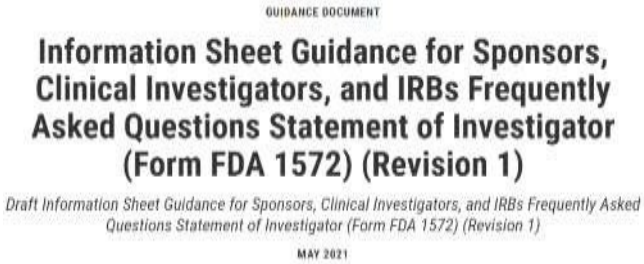
AUGUST 2023


GUIDANCE DOCUMENT

Clinical Investigator Administrative Actions - Disqualification

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

DECEMBER 2022


GUIDANCE DOCUMENT

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions Statement of Investigator (Form FDA 1572) (Revision 1)

Draft Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions Statement of Investigator (Form FDA 1572) (Revision 1)

MAY 2021

https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch

FDA Applications

- Investigational New Drug (IND) Application
- New Drug Application (NDA) and Biologics License Application (BLA)

Investigational New Drug (IND) Application

- Allows interstate shipping of product across state lines
- Allows initiation of clinical studies in humans
- Three types: investigator, emergency use, treatment
- Two categories: commercial, research
- Must include preclinical data, manufacturing information, clinical protocols and investigator information

https://www.fda.gov/drugs/types-applications/ investigational-new-drug-ind-application

IND Exemptions

- Product lawfully marketed in the U.S.
- Not intended to support new indication or significant labeling change
- Does not involve route of administration, dose, patient population, or other factor that significantly increases risk
- Investigation conducted in compliance with regulations for Institutional Review Boards, Informed Consent, and promotion

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-exemptions-ind-requirements

Purpose of INDs

- Provides data needed for FDA to ensure safety and rights of clinical study participants
- Ensures quality and adequacy of studies intended to provide evidence of the safety and effectiveness of medical products
- IND-opening study protocol goes into effect 30 days after received by FDA, unless notified earlier by FDA or FDA issues clinical hold

Clinical Hold

- Order issued by FDA to delay proposed clinical investigation or suspend ongoing investigation
  - No new subjects can be recruited and given the drug
  - Patients in study taken off therapy unless permitted to continue by FDA in interest of patient safety

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-clinical-hold

Grounds for Clinical Hold

Phase 1, 2, and 3:

- Unreasonable and significant risk of illness or injury
- Insufficient information to assess risk
- Investigator brochure is misleading, erroneous, or incomplete
- Clinical investigators not qualified
- Exclusion by gender if for life-threatening condition

Phase 2 and 3:

- Protocol deficient in design to meet stated objectives

Marketing Applications

- New Drug Application (NDA) under 505(b) of FD&C Act
- Biologics License Application (BLA) under 351(a) of the PHS Act
- Submission of information needed to support marketing approval of a new product or additional information for an already approved product

Definition of a Drug

- Defined in FD&C Act as:
  - (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary; and
  - (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
  - (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals
  - (D) articles intended for use as a component of any article specified in (A), (B), or (C).

Definition of a Biological Product

- Defined in Public Health Service Act as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.
- All biological products meet definition of drug.

Content of an NDA/BLA

- Chemistry, manufacturing, and controls
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavailability
- Microbiology (for anti-infectives)
- Clinical, statistical, and pediatric use
- Samples and labeling
- Case report forms and tabulations
- Legal information (e.g., patents, exclusivity, financial certifications)

Key Decisions for Drug Approval

- Whether the **drug is safe and effective** in its proposed use(s), and whether the benefits of the drug outweigh the risks
- Whether the drug's proposed **labeling is appropriate**, and what it should contain
- Whether the **manufacturing methods** used to maintain the drug's quality **are adequate** to preserve the drug's identity, strength, quality, and purity

https://www.fda.gov/drugs/types-applications/new-drug-application-nda

Challenge Question #1

For a drug that is lawfully marketed in the United States, an Investigational New Drug application is never required to conduct a clinical investigation using the drug.

True

False

Challenge Question #2

Which of the following is NOT a reason for a Clinical Hold?

A. Investigator brochure is incomplete

B. Insufficient information to assess risk

C. Investigation of drug for disease that manifests in childhood excludes children

D. Clinical investigators are not qualified

Summary

- FDA has been working to promote and protect public health for over 100 years
- Laws, regulations, and guidance provide a framework for the development and approval of drugs and biologics
- INDs allow FDA to evaluate whether clinical investigations are reasonably safe to proceed
- NDAs and BLAs are mechanism for FDA oversight of U.S. sale and marketing of drugs and biologics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