Structure and Mandate of FDA

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FDA

FDA Clinical Investigator Training Course
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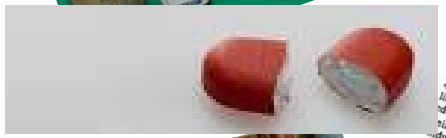
Mission of regulatory agencies

- Protection of people
  - Most countries in the world have regulatory institutions
  - Various levels of complexity

Why regulatory agencies?

Built on a legacy of failures:



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 participants surviving.

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.

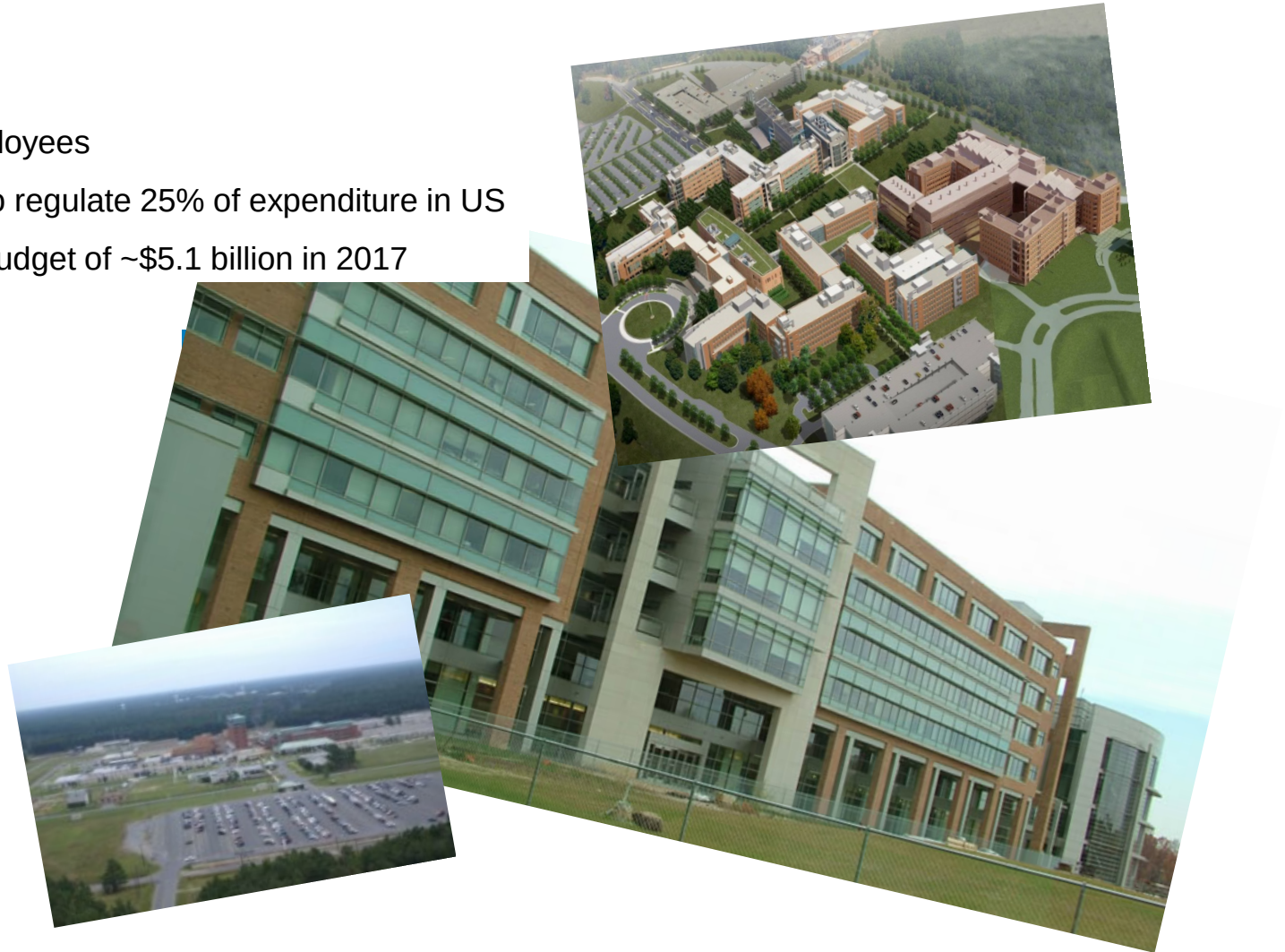
Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

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

Quick history

- 1902 - Biologics control act 1902
- 1906 - Pure food and drug act 1906
- 1912 - Prohibits false therapeutic claims (Sherman amendment)
- 1930 - Named FDA
- 1938 - Food drug and cosmetic act – prove safety
- 1951 - Codified “Prescription only” (Durham Humphrey amendment)
- 1962 - Required to prove effectiveness (Kefauver Harris amendment)

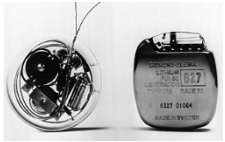
- 15,000 employees
- Estimated to regulate 25% of expenditure in US
- Operating budget of ~$5.1 billion in 2017



Three centers in FDA regulate human medical products

- CDER-drugs
- CBER-biologics
- CDRH-devices

Medical products

Drugs 	**Biologics** 	**Devices** 
Small molecules	Large molecules	
Generally synthetic	Derived from living organisms	Manufactured
Analytically simple	Analytically complex: vaccines, gene therapy, tissues and blood and cellular products	Engineering/physical: Catheters, prosthetics, pacemakers, defibrillators, in vitro diagnostics
Heat stable	Heat labile	
21CFR300	21CFR600	21CFR800

Code of Federal Regulations

21 CFR Sections
Parts 1-99
Part 14 Advisory Committees Part 50 Informed Consent Part 54 Financial Disclosure by Clinical Investigators Part 56 Institutional Review Boards (IRBs)
Part 300
Part 312 Investigational New Drug Application (IND) §312.20 Requirement for an IND §312.22 General principles of the IND submission §312.23 IND content and format §312.32 IND safety reporting §312.33 Annual reports §312.42 Clinical Hold §312.310 Emergency IND (E-IND)
Part 314 New Drug Application (NDA) §314.50 Content and format of an NDA §314.80 Postmarketing reporting of adverse drug experiences §314.126 Adequate and well-controlled studies §314.500 (Subpart H) – Accelerated Approval §316.20 (Subpart C) - Orphan drugs
Part 600 Biological License Application (BLA) **Part 800 Devices**

Investigational new drug application
(Protection of human subjects)

Investigational new drug application (IND) - (21 CFR 312)
- Required in order to initiate human studies
- Allows shipping of investigational drug for the purpose of conducting a clinical trial

Ensures:
- That studies are safe and ethical
- That they are likely to produce meaningful results
- Satisfactory monitoring and reporting of safety

Exemption (21 CFR 312.2(b)):
- Lawfully marketed drugs used in doses and populations that do not increase risk
- Not intended to support changes in labeling or advertising

Clinical hold (21 CFR 312.42):
- Studies can be delayed or halted by FDA for safety concerns

New drug application (NDA)
Biologics license application (BLA)

Requirements for a marketing application

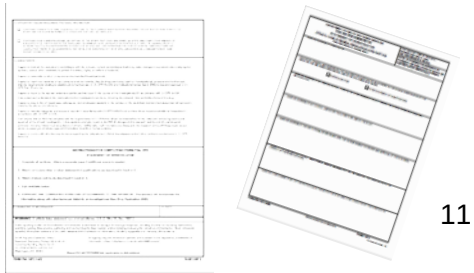
- Required components
- Safety reports

NDA includes, for example:

- Non-clinical studies: chemistry, in vitro, animal
- Efficacy and safety results from clinical studies performed under IND

If you are involved in a study under IND…..

- FDA needs to review the IND/study protocol to allow the study to proceed
- You need to be aware of responsibilities of investigators – see e.g., Form FDA 1572
- Informed consent, IRB review, safety reporting, reasonable expectation of a meaningful result

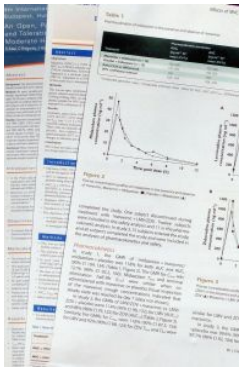


1572 commitments

- Comply with protocol
- Personally conduct/supervise investigation
- Informed consent and IRB review
- Report adverse experiences
- Read and understand investigator's brochure
- Ensure study staff are aware of responsibilities
- Maintain adequate records and make them available for inspection
- Ensure IRB oversight, and notify IRB of problems or changes

If you are involved in a study under IND…..

- Investigators brochure
  - FDA reviews along with the protocol in the IND submission
- On this basis you will have to decide if the study is safe and appropriate for your patients
  - Safety information
  - CMC-impurities, shelf-life, substance uniformity
  - Toxicology-general, geno, carcino, cardiac NOAELs
  - Clinical pharmacology-peaks, AUC's, metabolites, drug interactions, ADME



Pre IND meeting- product characteristics and plans for development

IND submission

IND review- clinical holds meeting

Review of Study designs and supporting safety and efficacy data

Sponsor has completed sufficient studies to support an application

IND safety reports

End of phase 2 meeting- discussion of the study material to be included in the application

NDA submission

Filing meetings- determine that the package is complete and can be reviewed

NDA review- clinical, clinical pharmacology, CMC, Toxicology, microbiology, safety, risk management, pediatrics, compliance, labeling to address all regulations

Investigator responsibilities, record keeping

Advisory committee-public presentation of the application and input from experts

Approval/complete response

Phase 4 study

Ongoing surveillance and epidemiology

Labeling update/warning letters to doctors

Withdrawal

Supplementary NDA

Different types of NDA submissions

- **505 (b) (1)**- full development program by sponsor including all primary phase 1, 2 and 3 data
- **505 (b) (2)-** contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (i.e. can refer to literature and to previous FDA findings relevant to the application)
- **505 J** -(generic pathway) contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product. (Based on chemistry and bioequivalence)
- **Subpart H** adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (e.g. HIV drugs)
- **Animal rule** - drug and biological product development when human efficacy studies are not ethical or feasible. e.g. anthrax prophylaxis

IDE (Investigational Device Exemption) 21CFR814

- ensures protection of human subjects in clinical trials (equivalent to IND for drugs)
- needed for “Significant Risk Device studies” (21 CFR 812.3(m))* (For in vitro diagnostics, when the result significantly affects patient treatment in a way that presents serious risks.)
- even if an IDE is not needed, informed consent and IRB review are often necessary. informed consent usually not needed for ‘leftover specimen ’ in vitro diagnostic studies.

*https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf

Medical Devices

- Unlike drugs and biologics, devices are divided into 3 classes depending on the type of information needed to ensure safety and efficacy.

Class I	Class II	Class III
e.g., cotton swabs	e.g., lab tests, most devices	e.g., defibrillators
General controls	General and special controls	
Exempt from premarket submission (with rare exceptions)	510 (k)	Premarket approval (PMA)

Pathways to approval/clearance of devices

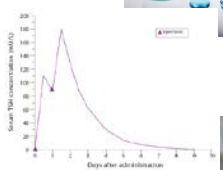
- 510(k) (21 CFR 807)
  - substantial equivalence to a predicate device
  - e.g., does a new pulse oximeter perform as well as an existing, cleared device.
  - 510(k) devices have a 90 day review and are cleared, not approved.
- De novo
  - a predicate device does not exist
  - Regulated as 510(k) if special controls can be designated that provide a reasonable assurance of the safety and effectiveness of the device
  - De novo devices have a 150 day review
- PMA (21CFR814)
  - class III devices and new devices where risk cannot be mitigated by special controls.
  - PMAs have a 180 day review and added regulatory oversight.

How does FDA decide?

- Scientific review
- CFR
- Guidances
- Advisory committees

Review team

- Chemistry
- Clinical pharmacology
- Toxicology
- Microbiology
- Clinical review
- Statistical review



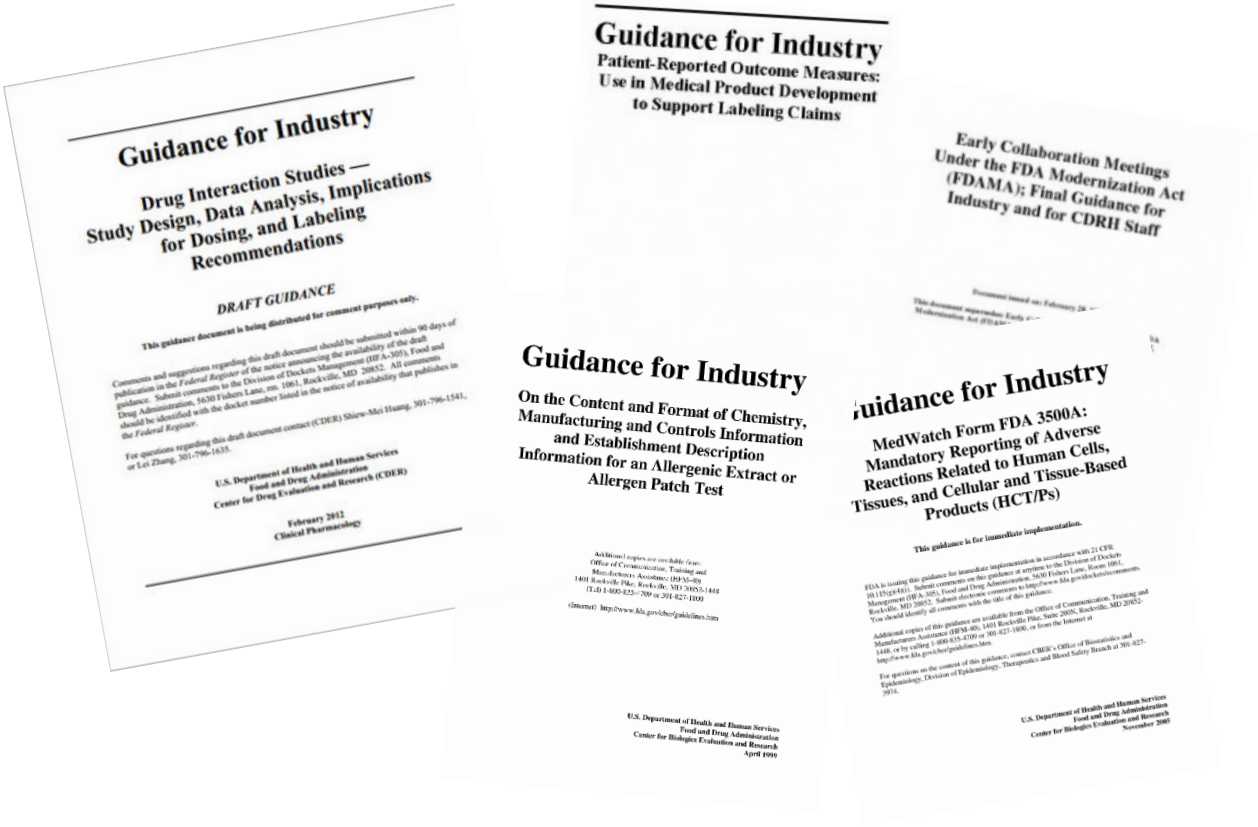
Substantial evidence of effectiveness

evidence consisting of adequate and well-controlled investigations, including clinical investigations,

by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved,

on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Guidance documents



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Guidance for Industry

On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test

Additional copies are available from:
Office of Communication, Training and Manufacturers Assistance (HFM-40)
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 1-800-835-4709 or 301-827-1800
(Internet) http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 1999

Early Collaboration Meetings Under the FDA Modernization Act (FDAMA): Final Guidance for Industry and for CDRH Staff

Document issued on: February 28

This document supersedes: Early [illegible]
Modernization Act (FDAMA)

uidance for Industry

MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by call[illegible] 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact CBER's Office of Biostatistics and Epidemiology, Division of Epidemiology, Therapeutics and Blood Safety Branch at 301-827-3974.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2005

Advisory Committee

Risk benefit

Unmet need

Convenience of administration

Reduced toxicity

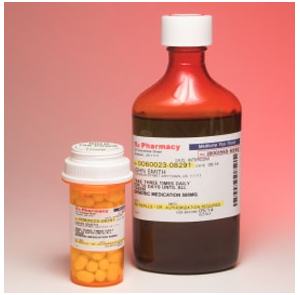
Superior efficacy

Toxicity

Inappropriate use

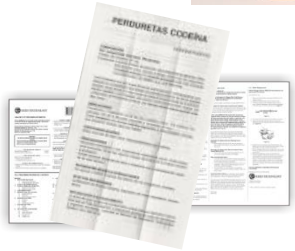
Drug-drug interactions

Product labeling



Contains information including

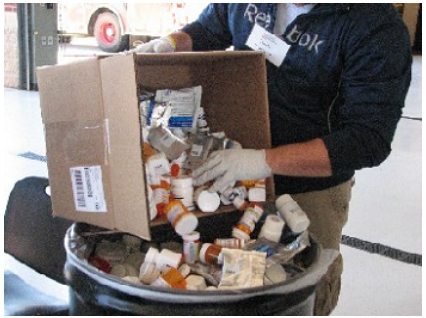
- Approved indication and use
- Dosage and administration
- Warnings and adverse reactions
- Drug interactions
- Use in specific populations
- Clinical studies



- Used by health care professionals and patients for information on safe and effective use
- Has implications for advertising and promotion

Drug failures

- 302 New molecular entity applications submitted to FDA between 2000 and 2012*
- 50% not approved on first submission
- 73.5% approved after one or more resubmissions
  - Efficacy deficiencies only 32%
  - Safety deficiencies only 26%
  - Safety and efficacy deficiencies 27%



- Sacks et al. JAMA 2014;311(4):378-384

Why did they not get approved?

Dose selection	15.9%
Study endpoints	13.2%
Inconsistent results (for different endpoints)	13.2%
Inconsistent results (for different trials or study sites)	11.3%
Poor efficacy compared to standard of care	13.2%
Data integrity	5.3%
Chemistry, manufacturing, labeling	1.3%

Adverse events seen in clinical trials that affected approval

Type of adverse event	Number of non-approvals
Cardiovascular	14
Overall mortality	11
hepatic	9
Neuropsychiatric	9
Hemostasis	6
gastrointestinal	5
Drug interactions	4
Infections	4
Allergy/immunology	4
Neoplasm	4
Renal	3
Musculoskeletal	2

Safety reasons that drugs were not approved

Theoretical risks (structure, mechanism of actions, class)	7.3%
Potential risk based on animal toxicology (e.g., carcinogenicity)	5.3%
Inadequate data in patients with renal/hepatic impairment	4.6%
Unsatisfactory data on QT prolongation	4.6%

What's new?

- Electronic platforms for clinical trials
  - The study machine

New technologies

- Mobile Technologies
- Electronic health records
- Electronic informed consent

New study design and analysis

- Adaptive trial designs
- Bayesian analyses
- Basket trials
- Pragmatic trials

U.S. FOOD & DRUG ADMINISTRATION