



Structure and mandate of FDA

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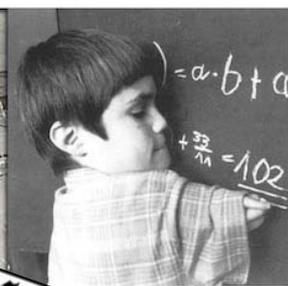
Mission of regulatory agencies



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



Why regulatory agencies? Built on a legacy of failures:



| State | Case Count | Deaths |
|---------------------|------------|----------|
| Florida (FL) | 4 | |
| Indiana (IN) | 11 | |
| Maryland (MD) | 5 | 1 |
| Michigan (MI) | 21 | 2 |
| Minnesota (MN) | 3 | |
| North Carolina (NC) | 2 | |
| Ohio (OH) | 1 | |
| Tennessee (TN) | 35 | 4 |
| Virginia (VA) | 23 | 1 |
| TOTALS | 105 | 8 |



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, and 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 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)



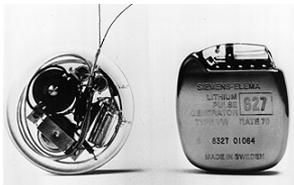
- 15,000 employees
- Estimated to regulate 25% of expenditure in US
- Operating budget of \$4.36 billion in 2012
- 223 field offices



Structure

- CDER-drugs
- CBER-biologics
- CDRH-devices
- CFSA-foods
- CVM-veterinary products
- NCTR - toxicology
- CTP-tobacco products

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 |
| <p>Part 14 Advisory Committees Part 50 Informed Consent Part 54 Financial Disclosure by Clinical Investigators Part 56 Institutional Review Boards (IRBs)</p> |
| Part 300 |
| <p>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)</p> |
| <p>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</p> |
| <p>Part 600 Biological License Application (BLA) Part 800 Devices</p> |



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

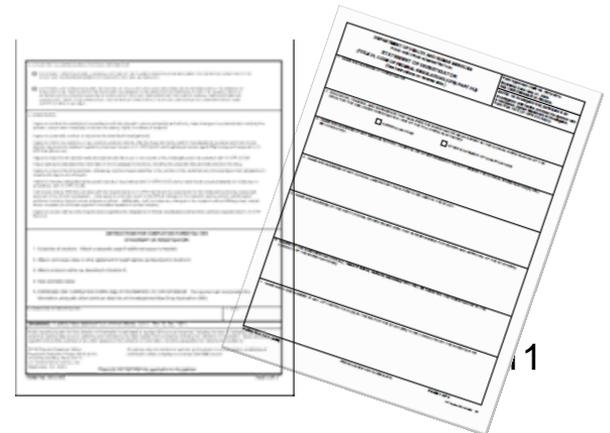
- Required components
- Safety reports

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

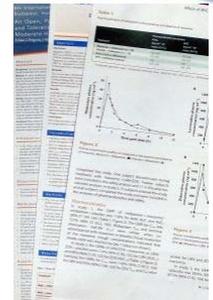


1572 commitments

- 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

Review of Study designs and supporting safety and efficacy data

IND review- clinical holds meeting

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

Supplementary NDA

Withdrawal

IDE (Investigational Device Exemption)

21CFR814

- ensures protection of human subjects in clinical trials (equivalent to IND for drugs)
- needed for studies of “Significant Risk Devices” (21 CFR 812.3) (Generally includes in vitro diagnostics where the result affects patient treatment.)
- Even if a IDE is not needed, informed consent is most often necessary.

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 | 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 standards can be followed that assure safe and effective use.
 - This usually means publishing a guidance document with clearance of the device.
- **PMA** (21CFR814)
 - class III devices and new devices where risk cannot be mitigated by special controls.
 - PMAs have a 120 day review and added regulatory oversight.

How does FDA decide?

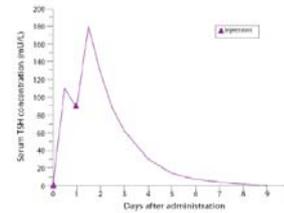
- Scientific review
- CFR
- Guidances
- Advisory committees



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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 2011
Clinical Pharmacology

Guidance for Industry
**Patient-Reported Outcome Measures:
Use in Medical Product Development
to Support Labeling Claims**

Additional copies are available from:
Office of Communication, Training and
Manufacturers Assistance (OFMA-40)
1401 Rockville Pike, Rockville, MD 20852-1448
(Toll) 1-800-835-4709 or 301-827-1800
(Internet) <http://www.fda.gov/oc/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 CDRII Staff**

Document issued on: February 28, 2008
This document supersedes Early Collaboration Meetings Under the FDA Modernization Act (FDAMA) Guidance for Industry and for CDRII Staff, February 2007.

Guidance 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/comments>. 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 (OFMA-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/oc/guidelines.htm>.

For questions on the content of this guidance, contact CDER'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

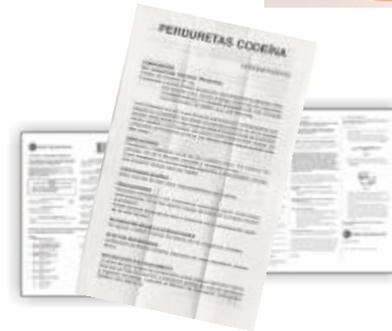
Inappropriate
use

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



Product failures

- About 50% of NMEs fail to get approved when first submitted to FDA
- Eventually more than 70% of NMEs are approved
- Demonstration of efficacy is more often a problem than demonstration of safety
- Common deficiencies:
 - choice of study endpoints
 - inconsistent results
 - problems with dosage selection
 - new safety signals
 - CMC problems
 - procedural problems with conduct of studies, data integrity



Program

- Today- phase 3 clinical studies
- Tomorrow- preclinical and early clinical studies
- Thursday- special topics and breakouts

