Structure and Mandate of FDA

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Objectives

- Provide a brief history of FDA
- Explain the regulatory processes for approval/clearance of drugs and medical devices
- Describe the roles of the Code of Federal Regulations, guidances and advisory committees

Why regulatory agencies?

Built on a legacy of public health failures:

- Safety
- Ethics
- Fraud
- Counterfeits and adulteration

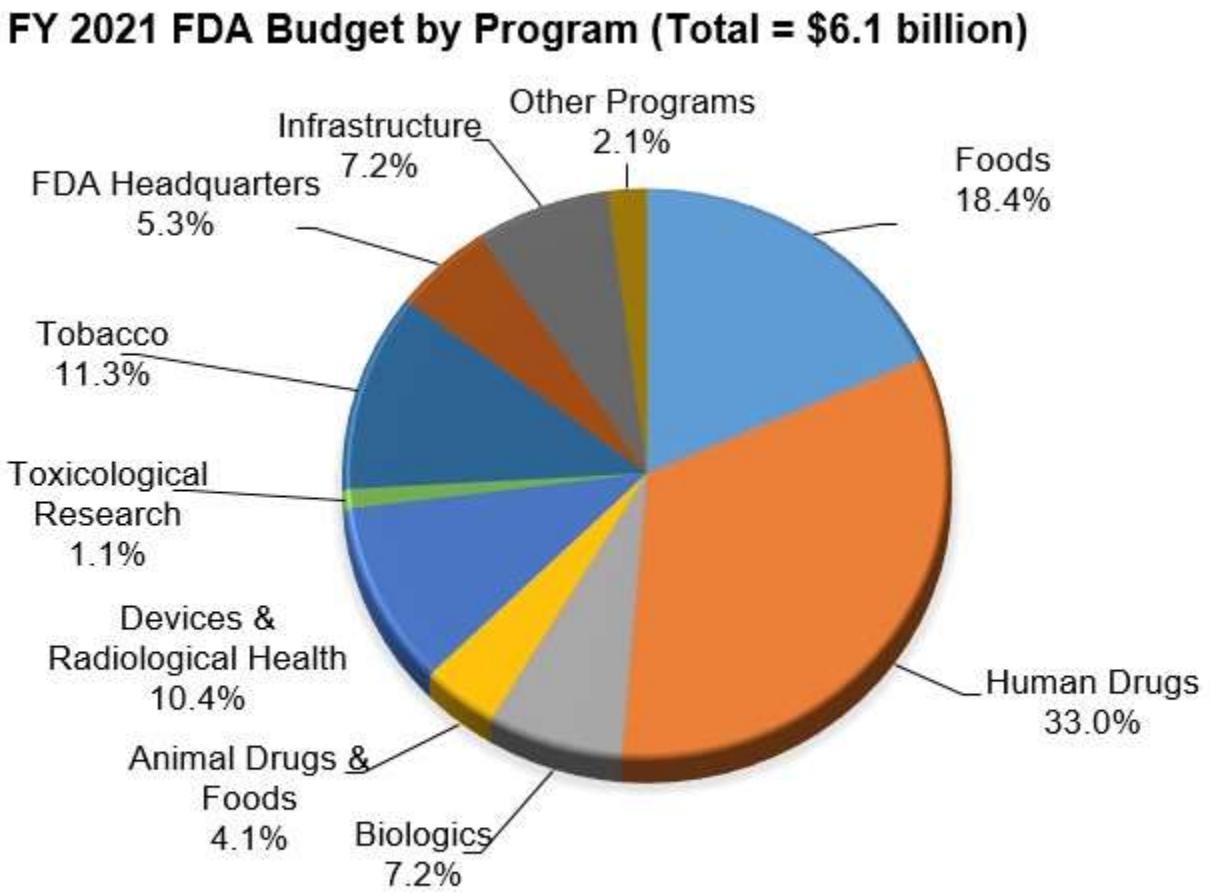
Quick History

- 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)
- 1992+ – User fees acts (PDUFA, MDUFA, GDUFA, BSUFA, OMUFA, ADUFA, tobacco user fees)

FDA Today

- **18,000 employees**
- **Estimated to regulate 20 cents per each dollar spent by US consumers**

FDA Budget



Notes: Infrastructure includes rent, rent related activities, FDA buildings and facilities, and White Oak consolidation. Other programs includes Export Certification and Color Certification Fund.

[Fact Sheet: FDA at a Glance | FDA]

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 across state lines 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

Investigational New Drug (IND) Application | FDA

IND Exemption

- The drug product is lawfully marketed in the United States.
- Not intended to support:
  - a new indication,
  - significant labeling change
  - significant change in the advertising
  - commercialization
- Does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk
- The investigation complies with IRB and Informed consent regulations

(21 CFR 312.2(b))

Clinical Hold

- Unreasonable and significant risk of illness or injury
- Clinical investigators not qualified
- Insufficient information to assess the risks to subjects
- Strong evidence of lack of effectiveness
- The investigator brochure is misleading, erroneous, or materially incomplete
- Protocol is deficient in design to meet its stated objectives.

- Studies that may interfere with other adequate and well controlled studies
- Drugs with better potential benefit:risk balances are available to the same patient

IND Application Procedures: Clinical Hold | FDA

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

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

Investigators Brochure

- Description of drug substance and formulation
- Summary of pharmacology and toxicology in animals and if known in humans
- Summary of prior information of safety and effectiveness in humans
- Possible risks and side effects
- Precautions and special monitoring

- On this basis you will have to decide if the study is safe and appropriate for your patients

Different types of NDA submissions

- **505 (b) (1)**- full development , all primary phase 1, 2 and 3 data
- **505 (b) (2)-** at least some of the information from studies not conducted by or for the applicant (literature or reference to relevant previous FDA findings)
- **505 J** -(generic pathway) product is identical to a previously approved product. (Based on chemistry and bioequivalence)
- **Subpart H** drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint other than survival or irreversible morbidity (e.g. HIV drugs)
- **Animal rule** - when human efficacy studies are not ethical or feasible. e.g. anthrax prophylaxis

Expedited Programs

Aimed to support drug development for serious conditions in need of new treatments

- Accelerated approval
  - based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
- Priority review:
  - 6 months compared with the 10-month standard review
- Fast-track:
  - Actions to expedite development and review
- Breakthrough
  - Intensive guidance on efficient drug development, Organizational commitment, Rolling review, Other actions to expedite review

IDE (Investigational Device Exemption)

21 CFR 812

- 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.

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

Classification of Medical Devices

- Unlike drugs and biologics, devices are divided into three classes based on the intended use and associated risks of the device.

Class I	Class II	Class III
Low Risk General controls	Moderate Risk General and special controls	Highest Risk General controls and premarket approval
e.g., bandages, manual stethoscopes	e.g., most lab tests, total knee replacements, powered wheelchairs	e.g., implantable pacemakers, spinal disc replacements
Exempt from premarket submission	510(k) (most common pathway to market)	Premarket approval (PMA)

Pathways to approval/clearance of devices

- 510(k) (21 CFR 807 Subpart E)
  - Substantial equivalence (SE) to a predicate device
- De Novo
  - A predicate device does not exist
- Premarket approval (PMA) (21 CFR 814)
  - Class III devices and new devices where risk cannot be mitigated by special controls
  - Valid scientific evidence must be presented to demonstrate a reasonable assurance of safety and effectiveness.

Harmonization

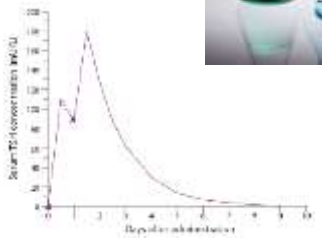
- **International Council for Harmonization (ICH)**
  - established in 1990.
  - goal is to produce consensus documents that support global approaches to drug development
  - approximately 40 guidelines listed on their website,
  - E6 is the guideline on good clinical practice, deals with the quality of clinical trials.
- **International Coalition of Medicines Regulatory Authorities (ICMRA)**
  - informal coalition of regulators
  - focused on aligning regulatory recommendations
  - more than 30 participating countries
- **Interagency agreements**
  - between FDA and other agencies allowing discussion and consultation
- **FDA guidances and regulations**
  - Released in draft
  - Announced in Federal register notices
  - Dockets are opened for public comment.

How does FDA decide?

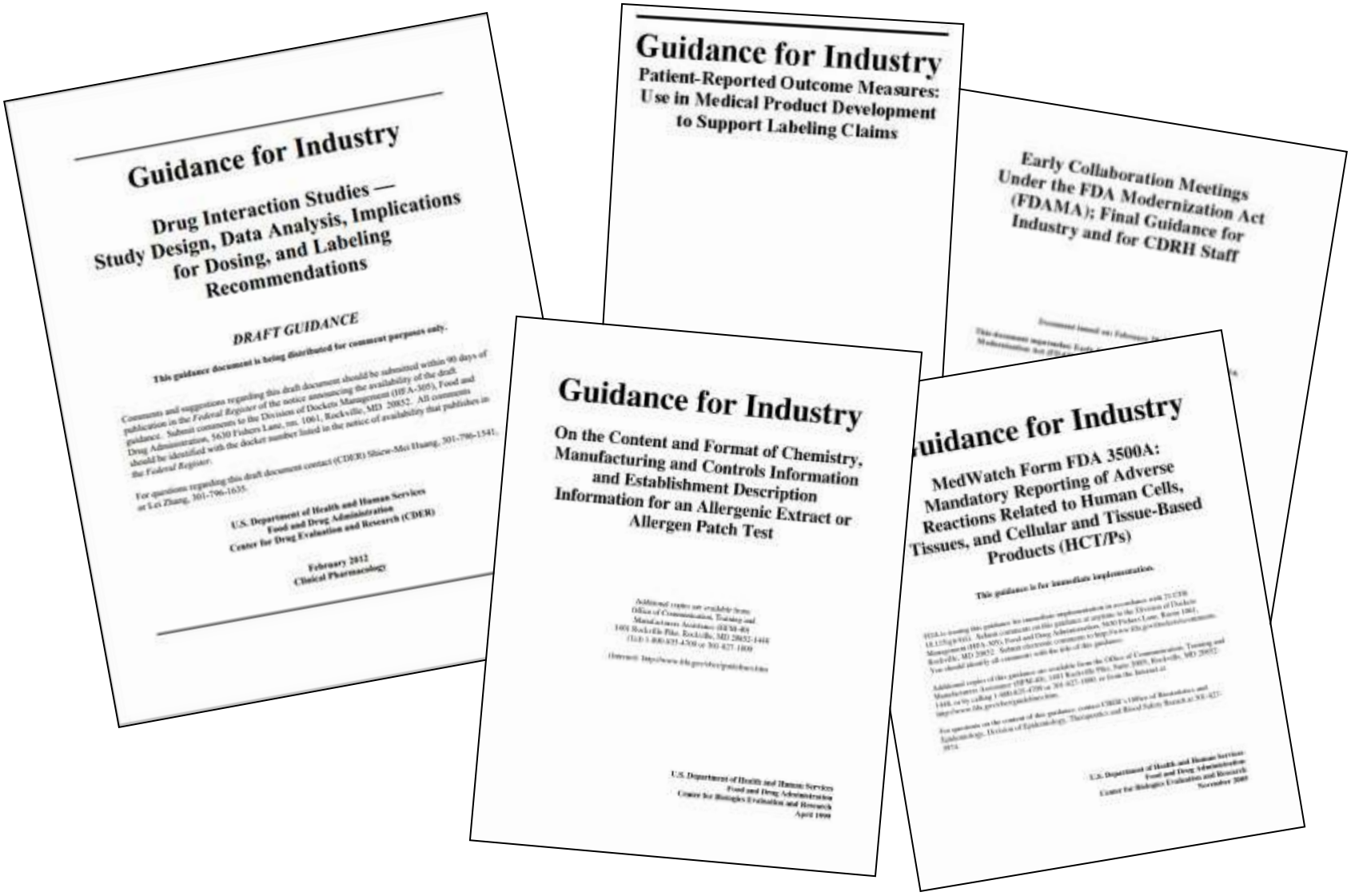
- Scientific review
- CFR
- Guidances
- Advisory committees

Review Team

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

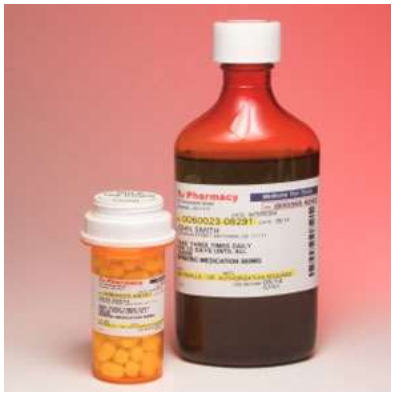


Guidance Documents



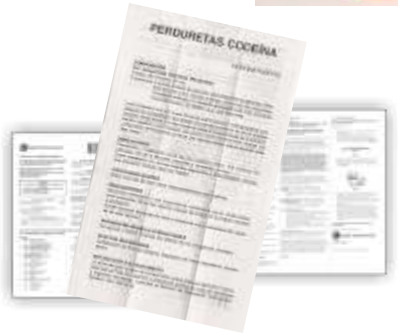
Advisory Committee

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

Questions

- An IND can be waived for a drug not approved in the USA, but approved in other countries T/F?
- Under what circumstances can the animal rule be used?
- What is accelerated approval?
- Drug labels contain data on clinical trials that supported approval T/F?