

Structure and mandate of FDA

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Objectives

- Provide a brief history of FDA
- Explain the regulatory pathways for approval/clearance of drugs and medical devices
- Describe the functions of the Code of Federal Regulations, guidances and advisory committees
- Explore reasons that drugs fail



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:









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)



Estimated to regulate 25% of expenditure in US

Operating budget of ~\$5.1 billion in 20





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 8



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 Review of Study designs and supporting safety and efficacy data meeting IND safety reports Sponsor has completed sufficient studies to support an application 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 Approval/complete response application and input from experts Phase 4 study Labeling update/warning letters to doctors Ongoing surveillance and epidemiology Supplementary NDA 15



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) 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.
 - Informed consent usually not needed for 'leftover specimen' in vitro diagnostic studies.

*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
 - Does a new pulse oximeter perform as well as an existing, cleared device?
 - 510(k) submissions have a 90 day review and are cleared or found not substantially equivalent (NSE)
- De Novo
 - A predicate device does not exist
 - Classified into Class I or Class II, if general and special controls can be designated that provide a reasonable assurance of the safety and effectiveness of the device
 - De Novo submissions have a 150 day review and are granted or declined
- 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.
 - 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-

tons regarding this draft document should be submitted within 90 days of Comments and suggestions regarding this draft document should be submitted within 90 days a publication in the Foderal Register of the notice anomalough the availability (50). Fod and Drag Abaria comments to the Division of Dockres Management (10 PA). Fod and Drag Abaria to the Abaria and Abaria (10 PA) and PA (10 PA) and PA abaria and PA (10 PA) an Yor 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 Drog Administration Center for Drog Evaluation and Research (CDER) February 2012 Clinical Pharmacology

Guidance for Industry

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

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

Inneed on : Falarmany 28.

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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 usyles are escalader frame ODise of Correnomization, Training and Monifectures Advisiones (UTM-40) 1401 Reviewille Film, Revolution, MD 2008257-1438 (Tel) 1-800-803-4509 er 501-827-1800

(Internet) http://www.ida.gov/cher/guidelines.htm

U.S. Department of Health and Hur S. Department of Ireann and Human Services Vood and Drug Administration Center for Biologies Evaluation and Research April 199

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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. ting their guidance for turnedbask implementation in accordinates with 21 CFR. We is shown a concernent on their guidance it anytime to the local according to Additional corpies of this pedance: we want to 100 pedance. Manufacturers Austing, (1004,401, 140) Recentle Professions 200N, Recentler, MD 2008(2) Interference and the second For questions on the content of this goldance, contact CBER's Office of Biotenthics and Fejaberhology, Davison of Fejaberhology, Therapaulics and Bioed Sufety Bearch at 301-827-3974.

U.S. Department of Hommann Hummins Food and Drug Administ Center for Biologics Evaluation and Re-



Advisory committee





Risk benefit

Unmet need

Convenience of administration

Reduced toxicity



Inappropriate use

Drug-drug interactions

Superior efficacy



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



Questions

- Under what circumstances may IND requirements be waived?
- Under what circumstances can the animal rule be used?
- What is accelerated approval?