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:
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

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

Review of Study designs and supporting safety and efficacy data

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 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.

Medical Devices

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

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g., cotton swabs</td>
<td>e.g., lab tests, most devices</td>
<td>e.g., defibrillators</td>
</tr>
<tr>
<td>General controls</td>
<td>General and special controls</td>
<td></td>
</tr>
<tr>
<td>Exempt from premarket submission (with rare exceptions)</td>
<td>510 (k)</td>
<td>Premarket approval (PMA)</td>
</tr>
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</table>
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 (21 CFR 814)**
  - 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.
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
<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose selection</td>
<td>15.9%</td>
</tr>
<tr>
<td>Study endpoints</td>
<td>13.2%</td>
</tr>
<tr>
<td>Inconsistent results (for different endpoints)</td>
<td>13.2%</td>
</tr>
<tr>
<td>Inconsistent results (for different trials or study sites)</td>
<td>11.3%</td>
</tr>
<tr>
<td>Poor efficacy compared to standard of care</td>
<td>13.2%</td>
</tr>
<tr>
<td>Data integrity</td>
<td>5.3%</td>
</tr>
<tr>
<td>Chemistry, manufacturing, labeling</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
### Adverse events seen in clinical trials that affected approval

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Number of non-approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>14</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>11</td>
</tr>
<tr>
<td>hepatic</td>
<td>9</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>9</td>
</tr>
<tr>
<td>Hemostasis</td>
<td>6</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>5</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>4</td>
</tr>
<tr>
<td>Infections</td>
<td>4</td>
</tr>
<tr>
<td>Allergy/immunology</td>
<td>4</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>4</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
</tr>
</tbody>
</table>
### Safety reasons that drugs were not approved

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical risks (structure, mechanism of actions, class)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Potential risk based on animal toxicology (e.g., carcinogenicity)</td>
<td>5.3%</td>
</tr>
<tr>
<td>Inadequate data in patients with renal/hepatic impairment</td>
<td>4.6%</td>
</tr>
<tr>
<td>Unsatisfactory data on QT prolongation</td>
<td>4.6%</td>
</tr>
</tbody>
</table>
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