

Clinical Trials and the Code of Federal Regulations

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The Development of Regulations

- 1906: Food and Drugs Act
 - In response to deaths from patent medicines
 - Prohibits mislabeling
- 1938: The Federal Food, Drug, and Cosmetic Act
 - A result of 107 deaths from elixir of sulfanilamide
 - Established requirement to demonstrate safety
 - Extends requirements to devices



The Development of Regulations (cont.)

- 1962: Kefauver-Harris Drug Amendments
 - Arose from Thalidomide incident
 - Requirement to prove effectiveness
 - First FDA requirement for written informed consent
 - Basis of current drug development regulation
- Current regulations/guidance: 1980s

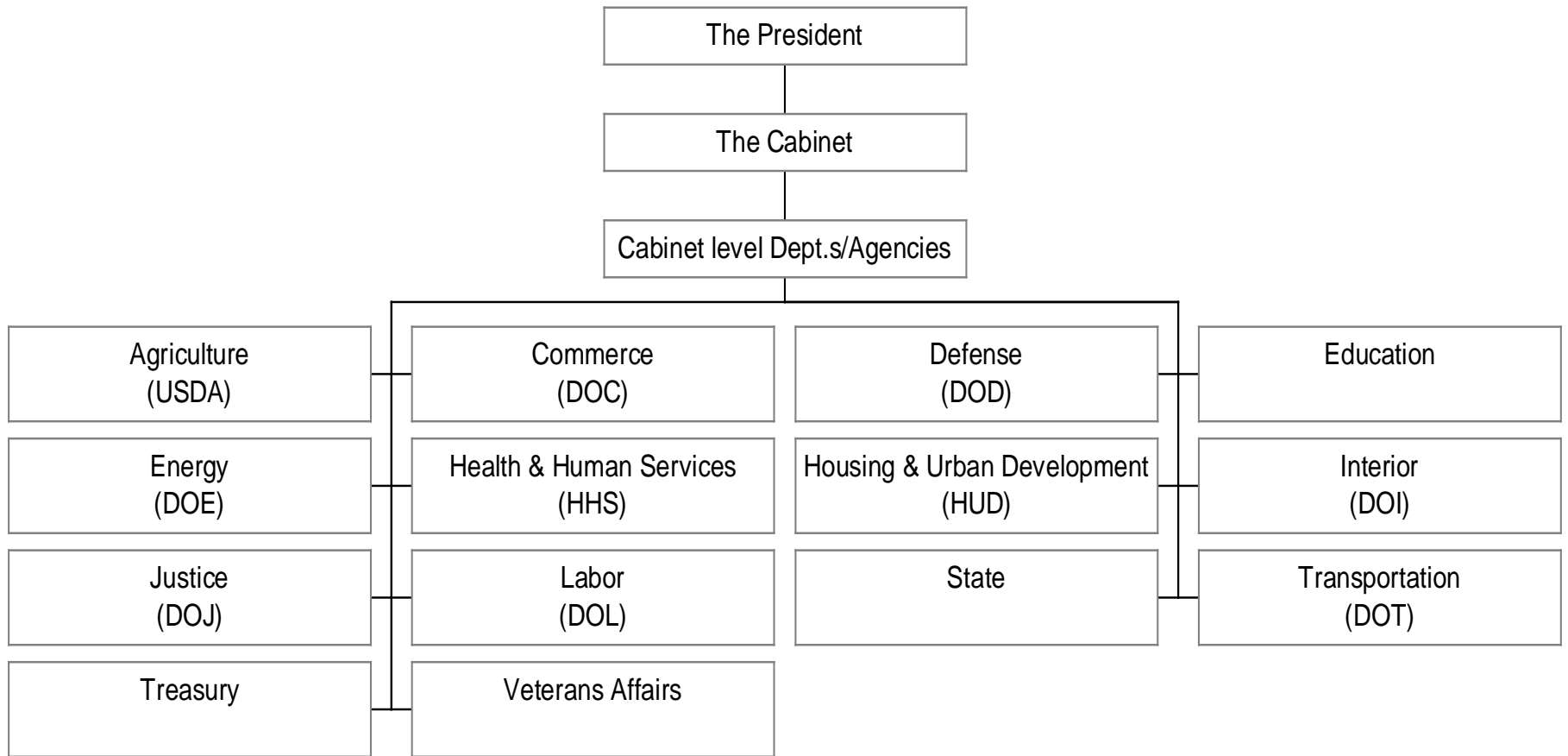


Federal Regulations

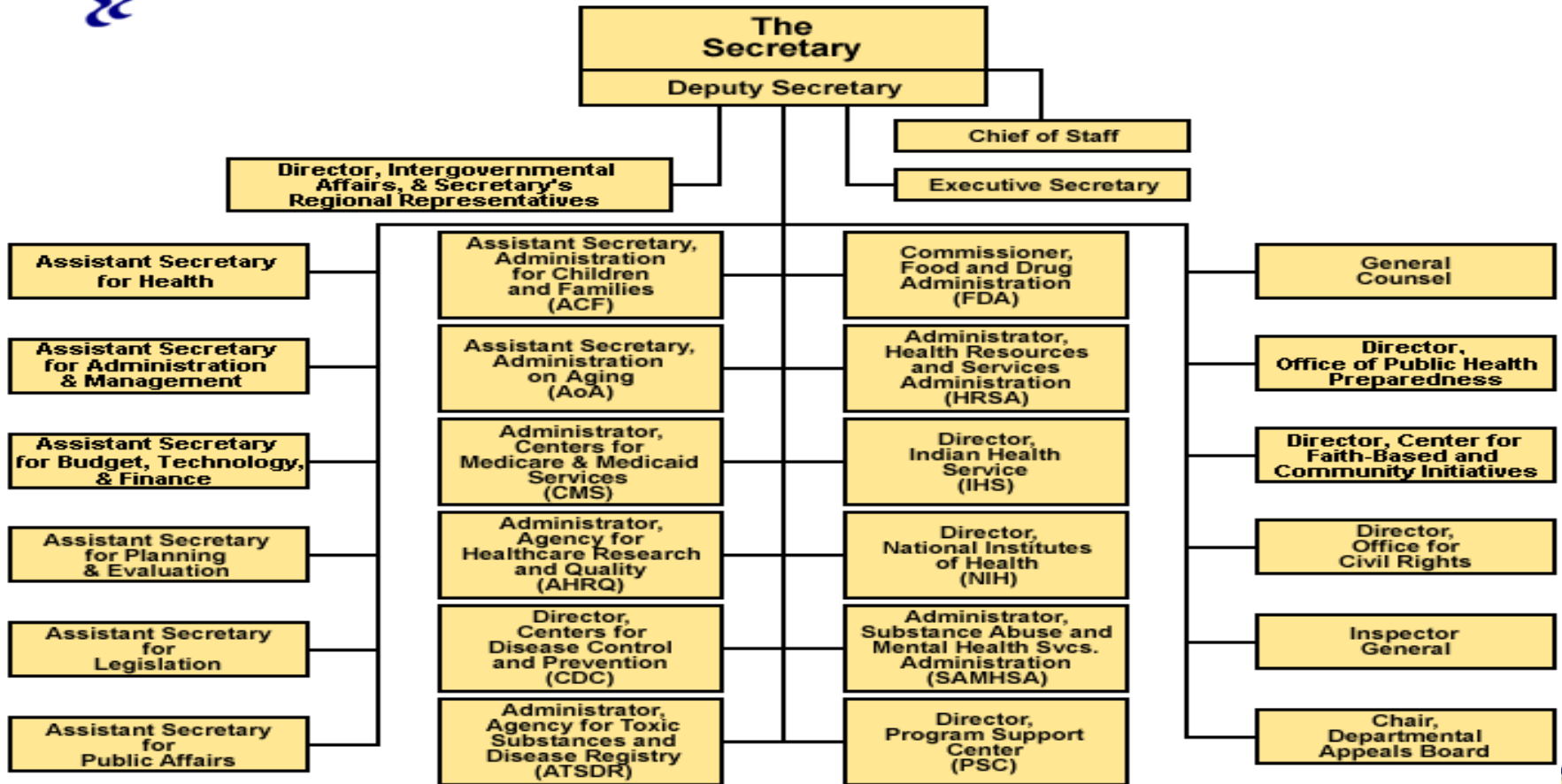
- Contained in the Code of Federal Regulations (CFR), Titles 21 and 45
- Enforced by:
 - the Food and Drug Administration (FDA)
 - Office of Human Research Protections (OHRP)
- Other relevant guidance:
 - International Conference on Harmonization (ICH) regulations
 - Guidelines (FDA, OHRP, ICH)



The Big Picture



HHS Organization



Regulatory Definitions

- Investigator: an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered
- Sponsor: a person who initiates a clinical investigation, but who does not actually conduct the investigation
- Institutional Review Board (IRB): any board, committee or other group formally designated by an institution to review research involving humans, to approve the initiation of and conduct periodic review of such research



Sponsor Responsibilities

- Obtaining information from the investigator
- Selecting qualified investigators
- Providing information to investigators
- Selecting qualified monitors
- Monitoring the trial
- Controlling the drug
- Maintaining records
- Reporting to the FDA



Sponsor: Collecting Information

- Site specific information:
 - Collected via p.1 of FDA form 1572 (312.53) (<http://forms.psc.gov/fda/ps1572.pdf>)
 - Name and address of investigator
 - Name and protocol number of study to be conducted
 - Name and address of any facility where the clinical investigation will be conducted
 - Name and address of any clinical laboratory facility to be used in the study
 - Name and address of the IRB that is responsible for review and approval of study
 - Name of subinvestigators (includes study coordinators)



Sponsor: Collecting Information (cont.)

- A commitment by the investigator that he or she will fulfill their responsibilities (p. 2 of FDA Form 1572)
- Collect information regarding investigator financial interests via FDA Form 3454 (54.4)



Sponsor: Selecting Investigators

- Sponsor will obtain a curriculum vitae or other statement of qualification of the investigator showing the education, training, and experience that qualifies the investigator (312.53)



Sponsor: Information to Investigators

- Provide investigators with protocol and Investigators' Drug Brochure (312.55)
- Promptly inform investigators of serious and unexpected adverse events (312.55)



Sponsor: Monitoring the Trial

- Must monitor progress of all clinical investigations (312.56)
- Must ensure trial is conducted in accordance with the protocol (312.50)
- Must monitor the safety of the drug (312.50)
- Must discontinue investigations if drug presents an unreasonable risk (312.50)



Sponsor: Monitoring the Trial (cont.)

- FDA Guideline for Monitoring of Clinical Investigations (January 1988)
 - selection of monitor
 - written monitoring procedures
 - preinvestigation visits
 - periodic visits
 - review of subject's records
 - record of monitoring visits



Sponsors: Controlling the Drug

- Sponsor only ships drug to investigators if have met all regulatory obligations prior to patient enrollment and provided for in IND (312.53)
- Must maintain records of drug receipt, shipment, and disposition (312.57)



Sponsors: Maintaining Records

- Records must be accessible for inspection by FDA (312.58)
- Records must be maintained for 2 years after drug approval or discontinuation of the IND (minimum) (312.57)
- Financial records kept for same period (54.6)
- May be required to keep records longer
 - International trial
 - Pediatric trial



Sponsors: Report to FDA

- Promptly inform FDA of serious and unexpected adverse events (312.32)
- Make annual progress reports to the FDA (312.50)
- Maintain an effective IND (312.50)



Contract Research Organizations

- Any or all of a sponsor's responsibilities may be transferred to a contract research organization (CRO) (312.52)
- The sponsor needs to inform the FDA in writing which responsibilities are performed by the CRO
- The CRO is held to the same regulations as the sponsor would for conducting these responsibilities



Obligations of Clinical Investigators

- Commit to obligations
- Conduct investigation appropriately
- Obtain approvals
- Control drug
- Maintain records
- Provide reports



Investigators: Commit to Obligations

- A commitment by the investigator that he or she:
 - will conduct the study in accordance with the relevant, current protocol
 - will comply with all requirements regarding the obligations of clinical investigators
 - will personally conduct or supervise the described investigation
 - will inform any patients, or any persons used as controls, that the drug is being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and institutional review board review and approval are met



Investigators: Commit to Obligations (cont.)

- A commitment by the investigator that he or she:
 - has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug
 - will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 312.64
 - will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments



Investigators: Commit to Obligations (cont.)

- A commitment by the investigator that he or she (cont.):
 - will be responsible for the initial and continuing review and approval of the clinical investigation and that investigator will report to the IRB promptly:
 - all changes in research activity
 - all unanticipated problems involving risks to subjects
 - will provide a list of the names of subinvestigators who will be assisting in the conduct of the study
- Commitment obtained via investigator signature of p.2 of FDA form 1572 and copy provided to sponsor and FDA



Investigators: Conduct Investigation

- Conduct in accordance with (312.60):
 - Protocol
 - Investigator's statement
 - IRB regulations
 - Consent regulations



Investigators: Obtain Approvals

- Must obtain IRB approval of protocol and informed consent form (312.66)



Investigators: Control Drug

- Obtain consent of each subject to whom drug is administered prior to participation in the study (312.60)
- Administer drug only to subjects under his or her supervision (312.61)
- Maintain adequate records of drug disposition (312.62)
- Store drug in a secure, locked cabinet with limited access (312.69)



Investigator: Maintain Records

- Maintain adequate and accurate case histories (312.62)
- Records must be maintained for 2 years after drug approval or discontinuation of the IND (312.62)
- Permit access to FDA for inspection (312.68)



Investigator: Reporting

- Submit annual progress reports to sponsor (312.64)
- Promptly report related adverse events to sponsor (312.64)
- Provide sponsor with a final report at study completion (312.64)
- Report to sponsor financial disclosure (312.64)



Investigator IND

- The Investigator is the “Sponsor” when the Investigator writes his/her own protocol (Sponsor-Investigator)
- The Investigator is responsible for adhering to all appropriate Federal Regulations pertaining to the Sponsor AND the Investigator (312.3)

