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US FDA: CMC Issues for INDs

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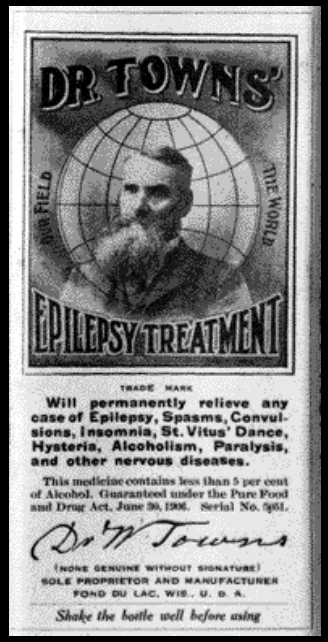
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies

Basis for regulation of INDs

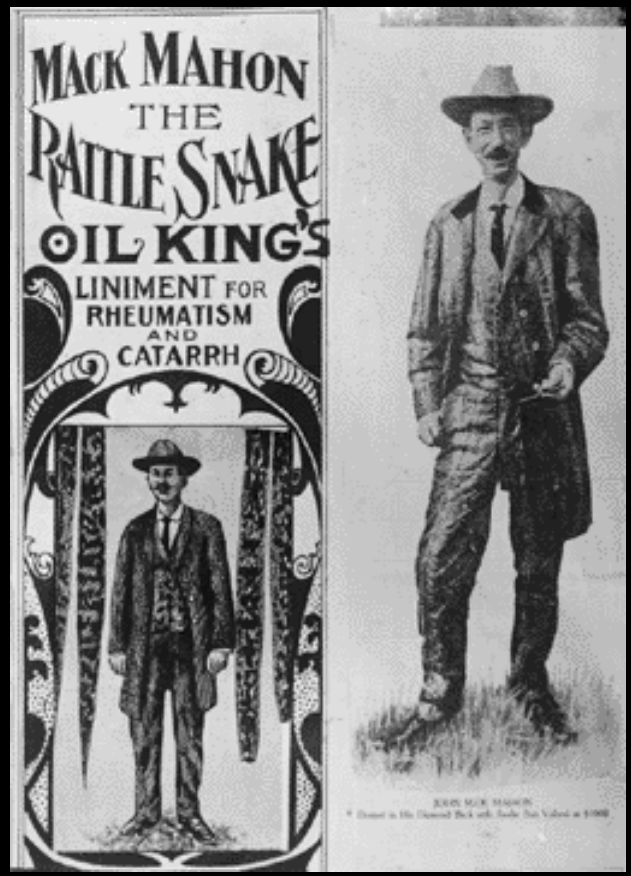
- **Statutes: THE LAW --- passed by Congress and signed by the President**
  - 42 USC 262 (United States Code)
- **Regulations: details of the law --- written by the Agency and approved by the Executive Branch**
  - 21 CFR 312 (Code of Federal Regulations)
- **Guidance: the Agency's interpretation of the Regulations --- written and approved within the Agency**
  - 68 FR 49488 (Federal Register)

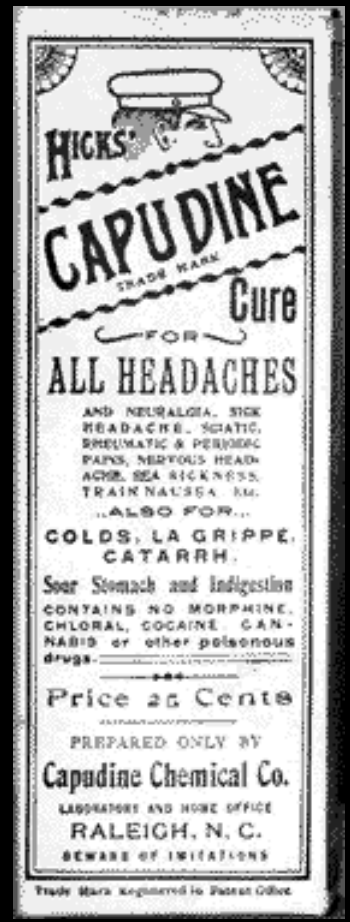


Dr. Mixer's Condition
After Cured by
his Cancer and Scrofula Syrup.

DRS. MIXER,
SOLE MANUFACTURERS
AND PROPRIETORS OF
SPECIAL TREATMENT GIVEN
MIXER'S CANCER AND SCROFULA SYRUP
Cancer, Tumors, Erysipelas, Abscesses, Ulcers, Fever Sores, Goiter, Catarrh, Salt Rheum, Scald Head, Piles, Rheumatism, and ALL BLOOD DISEASES.
The World Renowned
BLOOD PURIFIER.
ESTABLISHED 1862

DR. CHAS. W. MIXER,
GEN'L MANAGER.
Not a Physician.





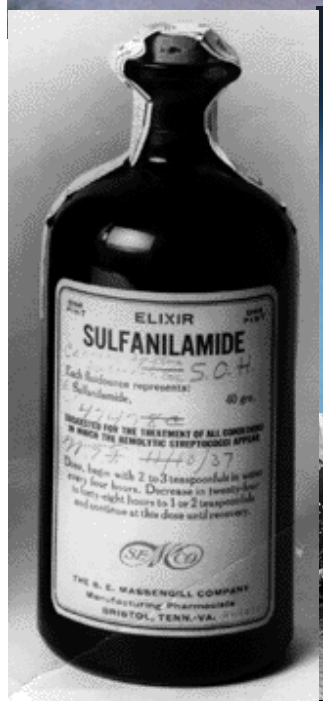
Drug and Biologics Law

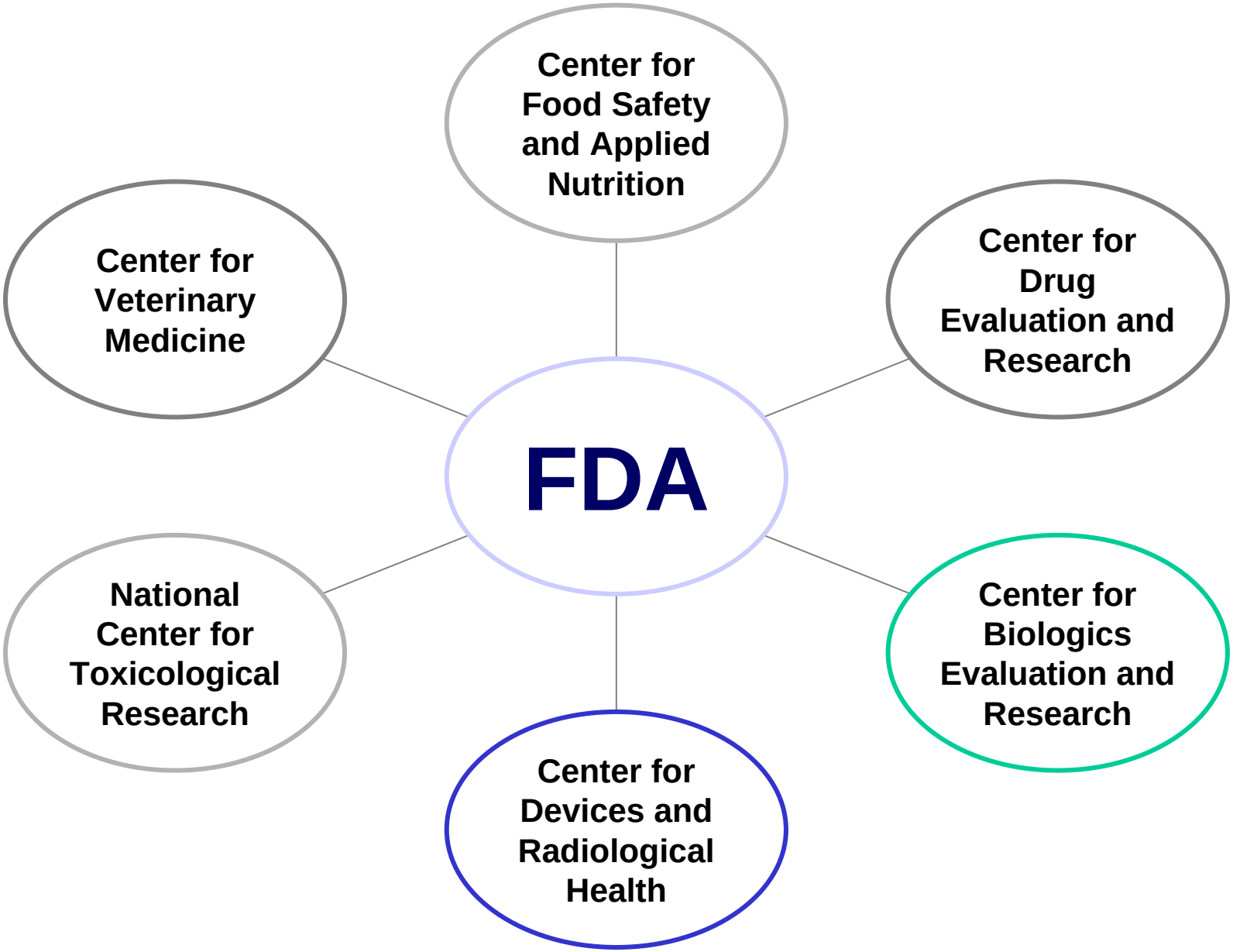
1902 Biologics Control Act authorizes regulations to ensure purity and safety of serums, vaccines, and similar products

1938 Food, Drug, and Cosmetic Act required new drugs to be shown safe before marketing. It also authorized factory inspections and other provisions.

1944 PHS Act incorporates provisions for biologics regulation. Outlines licensing requirements that are independent from pre-marketing requirements for drugs.

1962 FD&C Act Amendments required drug manufacturers to prove the effectiveness of their products before marketing them and allowed FDA to regulate investigational studies.




Center for Food Safety and Applied Nutrition
Center for Veterinary Medicine
Center for Drug Evaluation and Research
FDA
National Center for Toxicological Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

Premarket approval pathways

- **Biologics**
  - BLA – Biologics License Application
- **Drugs**
  - NDA – New Drug Application
  - ANDA – Abbreviated New Drug Application
- **Devices**
  - PMA – Premarketing Application
  - HDE – Humanitarian Device Exemption
- **Combination products**

Drug and Biologics Marketing Regulations

- **21 CFR parts 210, 211, 225, & 226**
  - Good manufacturing practices for drugs and biologics
- **21 CFR parts 600, 601, & 610**
  - Biological products regulations
- **21 CFR parts 201, 202, 203, 314**
  - Prescription drug regulations
- **21 CFR part 25**
  - Environmental impact considerations

Investigational studies

- **Biologics**
  - IND – Investigational New Drug application
- **Drugs**
  - IND – Investigational New Drug application
- **Devices**
  - IDE – Investigational Device Exemption
- **Combination products**

Regulations For INDs

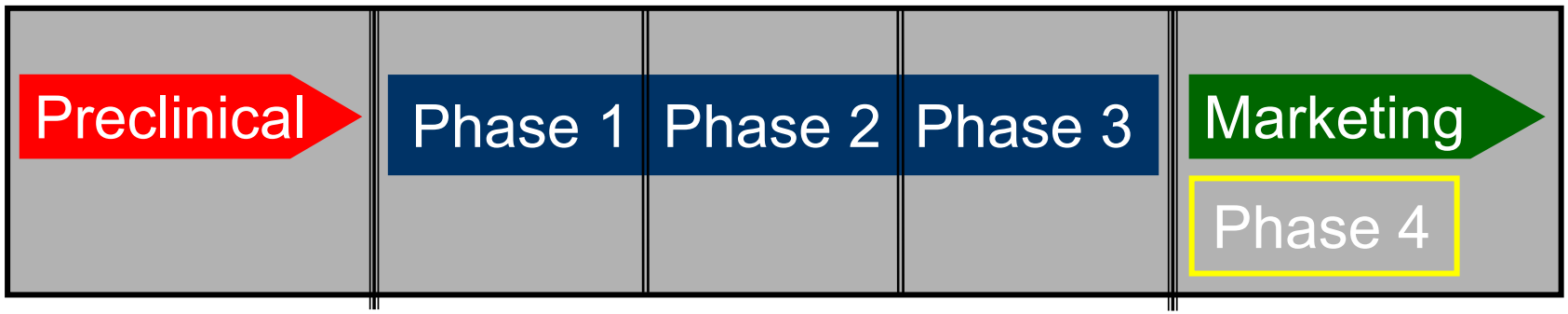
21 CFR 312

Investigational New Drug Application

National Archives and Records Administration

code of federal regulations

What are the phases of investigation?

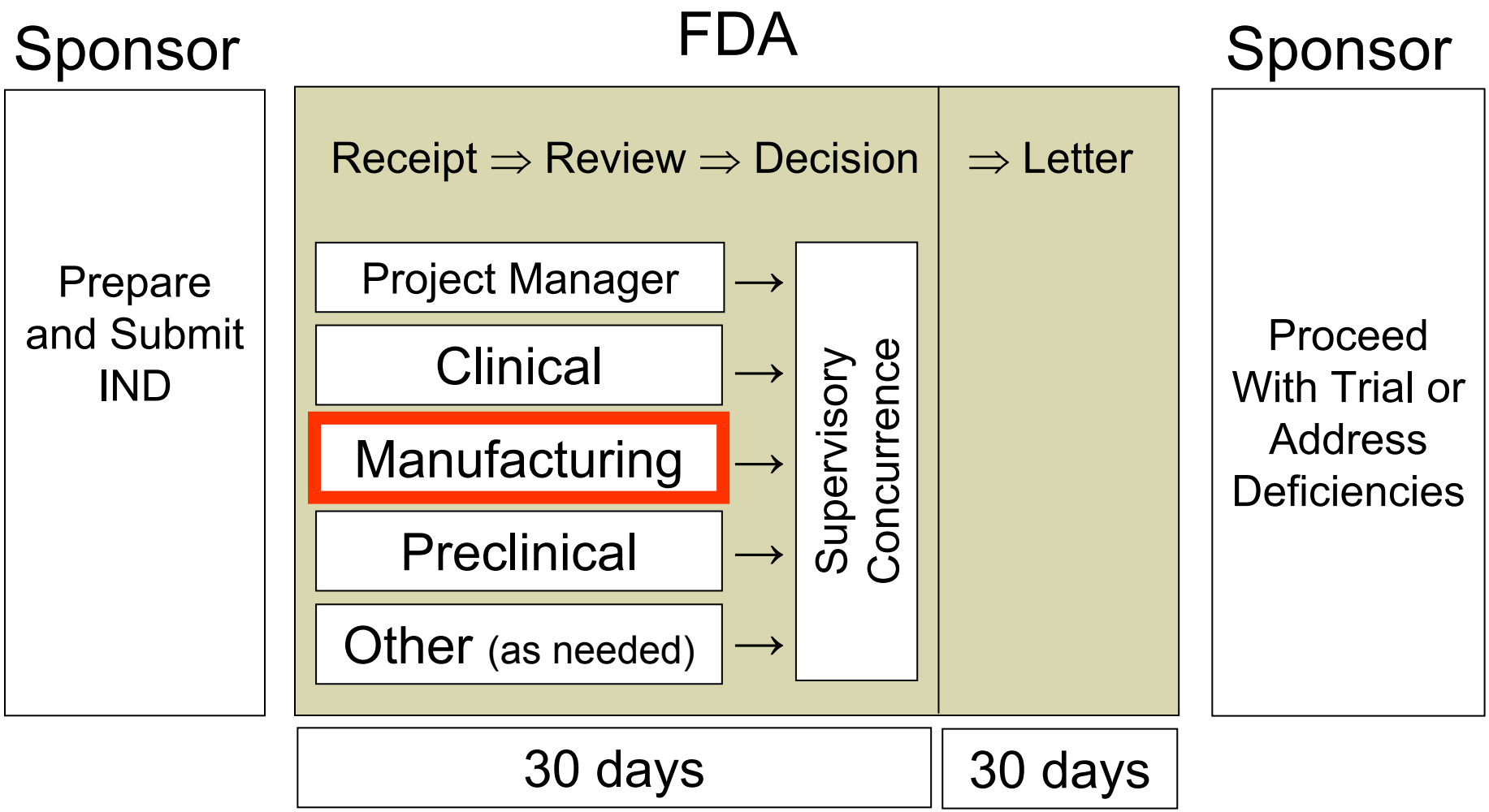


- Phase I: Designed to evaluate safety and side effects
- Phase II: Designed to evaluate safety and explore efficacy and dose ranging
- Phase III: Expanded study designed to obtain efficacy and safety data for approval
- Phase IV: Post marketing commitments to monitor safety and efficacy

What are the elements of an IND application?

☐	Form FDA 1571	21 CFR 312.23(a)(1)
☐	Table of Contents	21 CFR 312.23(a)(2)
☐	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
☐	Investigator's brochure	21 CFR 312.23(a)(5)
☐	Protocols	21 CFR 312.23(a)(6)
☐	Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
☐	Pharmacology and toxicology data	21 CFR 312.23(a)(8)
☐	Previous human experience	21 CFR 312.23(a)(9)
☐	Additional information	21 CFR 312.23(a)(10)

Initial IND Review Process



IND Review criteria

- **Clinical Hold Criteria (21 CFR 312.42)**
  - Risks are unreasonable and significant
  - Investigators not qualified
  - Investigator brochure false or misleading
  - Insufficient information to assess risk
  - Gender exclusion for a condition that occurs in both men and women

CMC Information for INDs:
Starting material

- **Choose an appropriate starting material**
  - Appropriate screening and testing of donors
    - See DE rule and guidance
  - Perform all required testing on your cell bank
    - Sterility, mycoplasma, viral testing (in vivo, in vitro, specific viruses)
    - Identity testing (species origin, markers, activity, purity, etc)
    - Stability (maintain desired activity upon thaw and passage)
    - Propagation, containers, labeling, storage
- **Ensure that your starting material is consistent**
  - Make sure your cell line is stable
  - Account for and determine how to control individual patient variability

CMC Information for INDs:
Manufacturing

- **Choose and qualify your reagents**
  - Ensure that reagents will perform as desired in the manufacturing process
  - Ensure clinical quality reagents (safety, purity, potency/activity)
  - Document reagent quality (in-house testing or COA)
- **Establish adequate facility and equipment performance standards and monitoring plans**

CMC Information for INDs:
Manufacturing process

- **Choose a robust manufacturing process**
  - Establish standard operating procedures (SOPs)
  - Establish batch records
- **Qualify your facilities**
- **Do performance runs to ensure process consistency**
- **Establish procedures to prevent:**
  - Product mix-ups
  - Product cross-contamination
- **Ensure process safety**
  - Qualify procedure for killing of tumorigenic cells
  - Validate viral clearance methods

CMC Information for INDs:
Product quality testing

- **In-process testing**
  - Design to assess process and product quality
- **Final product testing**
  - Perform on the final product, not intermediate
  - Establish proper specifications
    - Ensure the safety and consistency of product lots
    - Base acceptance criteria on experience
    - Determine the criteria for acceptable product
    - Should agree with current FDA standards

CMC Information for INDs:
Other

- **Include a plan for post infusion sterility failure:**
  - Notification of physician and patient.
  - Identification and sensitivity testing of the microbial contaminant.
  - Description of additional patient monitoring that will be conducted as a result of the event.
  - Investigation and potential corrective action
  - Reporting of the incident to the IRB and FDA
- **Have a quality assurance program**
- **Provide stability data to justify storage and holding times**
- **Make sure cross-references are accurate and relevant**

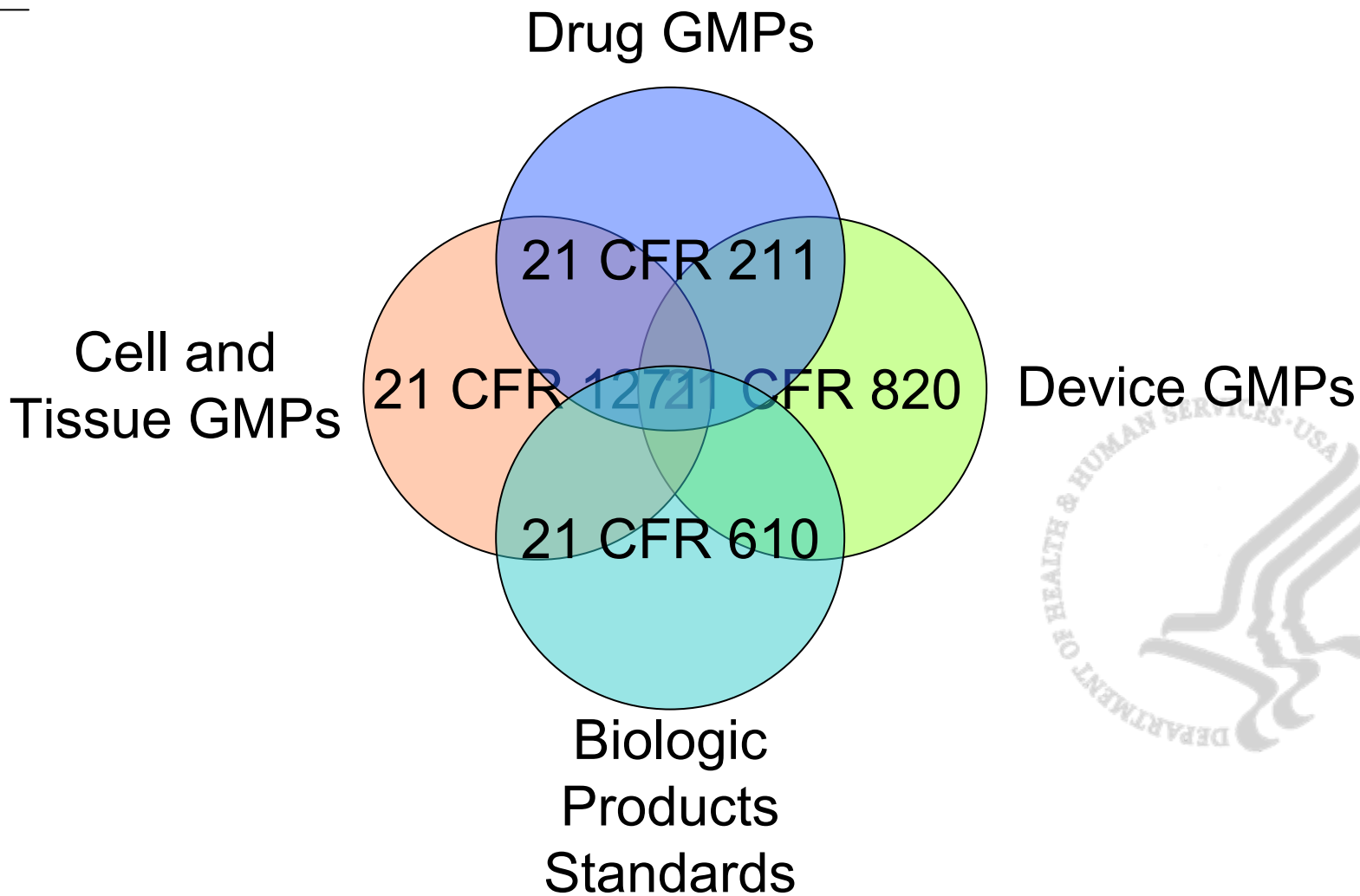
Common Cell and Gene Therapy IND Deficiencies

- **Analysis of FDA comments in ~100 Clinical Hold Letters issued 2002-2005**
- **Cytotherapy. 2008;10(3):312-6**
  - INDs Submitted To FDA That Are Placed On Clinical Hold: Experience of the Office of Cellular, Tissue, and Gene Therapies. Keith Wonnacott, Deborah Lavoie, Robert Fiorentino, Maritza McIntyre, Ying Huang, Steven Hirschfeld.

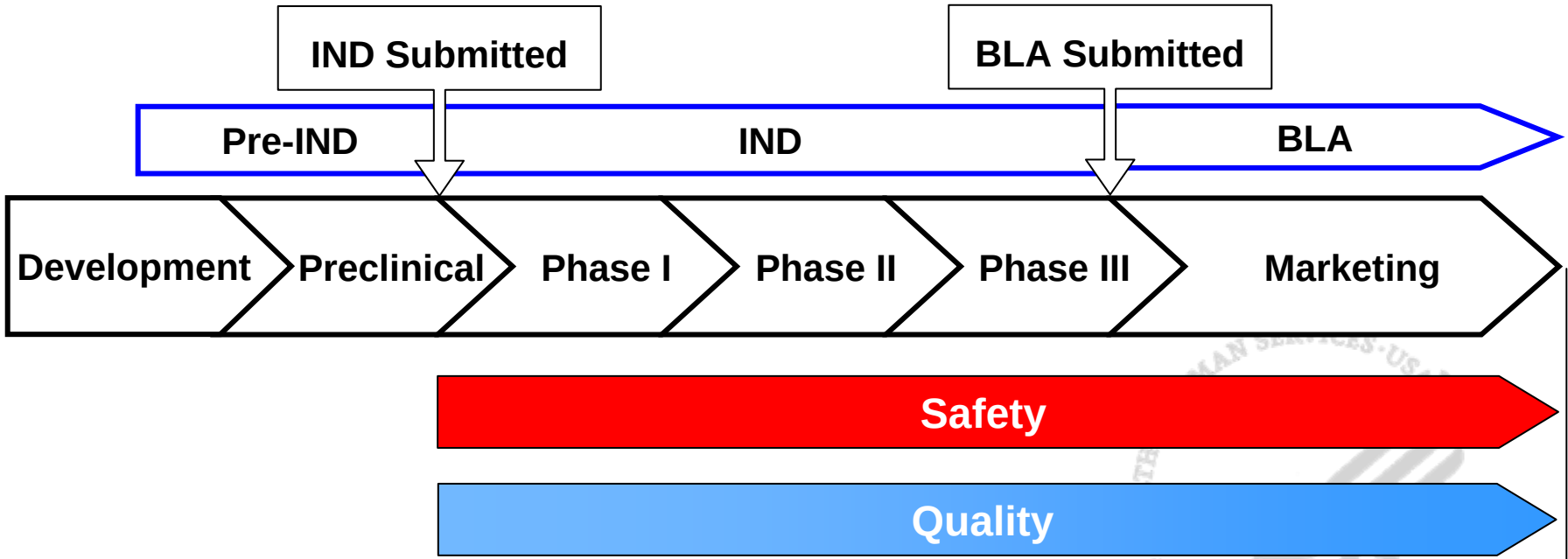
Summary

- FDA regulates both investigational and marketing applications
- Information about the process in US is contained in regulations and guidance documents
- Detailed manufacturing information is needed during product development
- Communicate with the FDA throughout your product development

GMPs for Drugs and Biologics



Manufacturing Expectations During Product Development



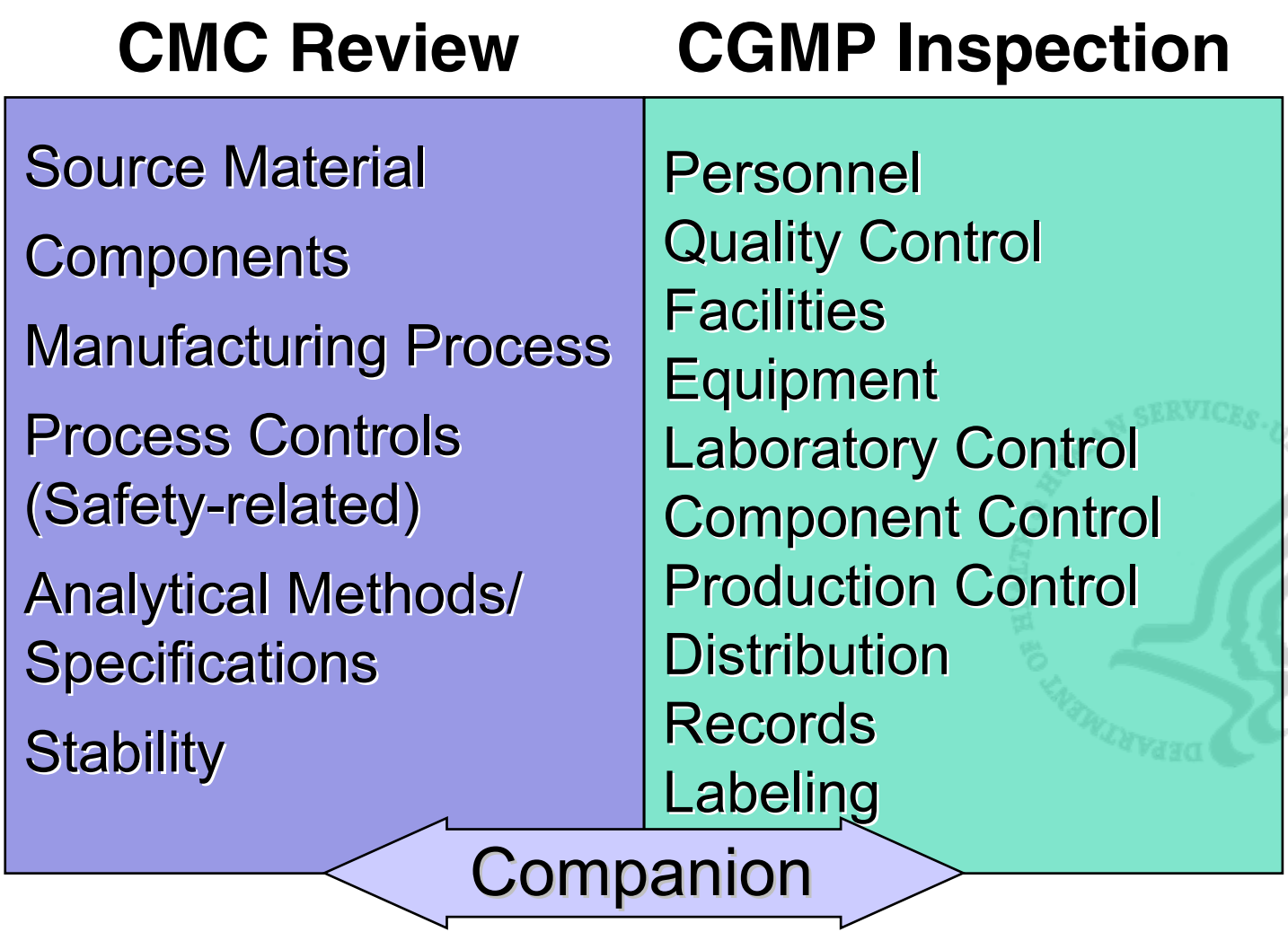
Principles of GMP apply throughout clinical manufacturing

Regulatory requirements depend on the stage of development

FINAL RULE: GMP and Investigational New Drugs (http://www.fda.gov/cber/rules/gmpind.pdf)

- **Exempts most Phase 1 studies from compliance with regulations in 21 CFR Part 211**
  - EXCEPT when drug: (1) has already been made available for use in Phase 2 or 3 study, or (2) has been lawfully marketed
- **GMP will still be required; appropriate to early IND**
  - Development of well-defined written procedures
  - Adequate control of equipment/manufacturing environment
  - Accurate/consistent data recording from manufacturing (including testing)
- **Guidance published**
  - http://www.fda.gov/cder/guidance/GMP%20Phase1IND61608.pdf

Ensuring GMP Compliance



Contact Information

Cellular product manufacturing questions

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General CBER Issues

Office of Communication, Training & Manufacturers Assistance
Manufacturers Assistance and Technical Training Branch

Telephone: 800-835-4709 or 301-827-1800
E-mail: matt@cber.fda.gov
Internet: http://www.fda.gov/cber/manufacturer.htm