US FDA: CMC Issues for INDs

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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)
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.
U.S. Food and Drug Administration

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Center for Veterinary Medicine

Center for Food Safety and Applied Nutrition

National Center for Toxicological Research

Center for Drug Evaluation and 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
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?

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**Initial IND Review Process**

**Sponsor**
- Prepare and Submit IND

**FDA**
- Receipt $\Rightarrow$ Review $\Rightarrow$ Decision $\Rightarrow$ Letter
  - Project Manager
  - Clinical
  - Manufacturing
  - Preclinical
  - Other (as needed)
  - Supervisory Concurrency

**Sponsor**
- Proceed With Trial or Address Deficiencies

30 days
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
  - 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

Drug GMPs

Cell and Tissue GMPs

Biologic Products Standards

Device GMPs

21 CFR 211

21 CFR 1271

21 CFR 820

21 CFR 610
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
### Ensuring GMP Compliance

#### CMC Review
- Source Material
- Components
- Manufacturing Process
- Process Controls (Safety-related)
- Analytical Methods/Specifications
- Stability

#### CGMP Inspection
- Personnel
- Quality Control Facilities
- Equipment
- Laboratory Control
- Component Control
- Production Control
- Distribution
- Records
- Labeling

### Companion
Contact Information

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General CBER Issues
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Manufacturers Assistance and Technical Training Branch

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