Taking a Vaccine into the Clinic: Administrative Process & Pitfalls of IND Applications

Jon R. Daugherty, Ph.D.
Commander, USPHS
Office of Vaccines
Research & Review

ASTMH
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IND Topics

- Statutes & regulations
- Regulated process
- IND content & format
- IND common pitfalls
- FDA guidance

Statutes

- Federal Food Drug & Cosmetic Act (21 USC 301-392)
  - ✓FDAMA, November 12, 1997
- Public Health Service Act (42 USC 262 Section 351
- Code of Federal Regulations

Regulations

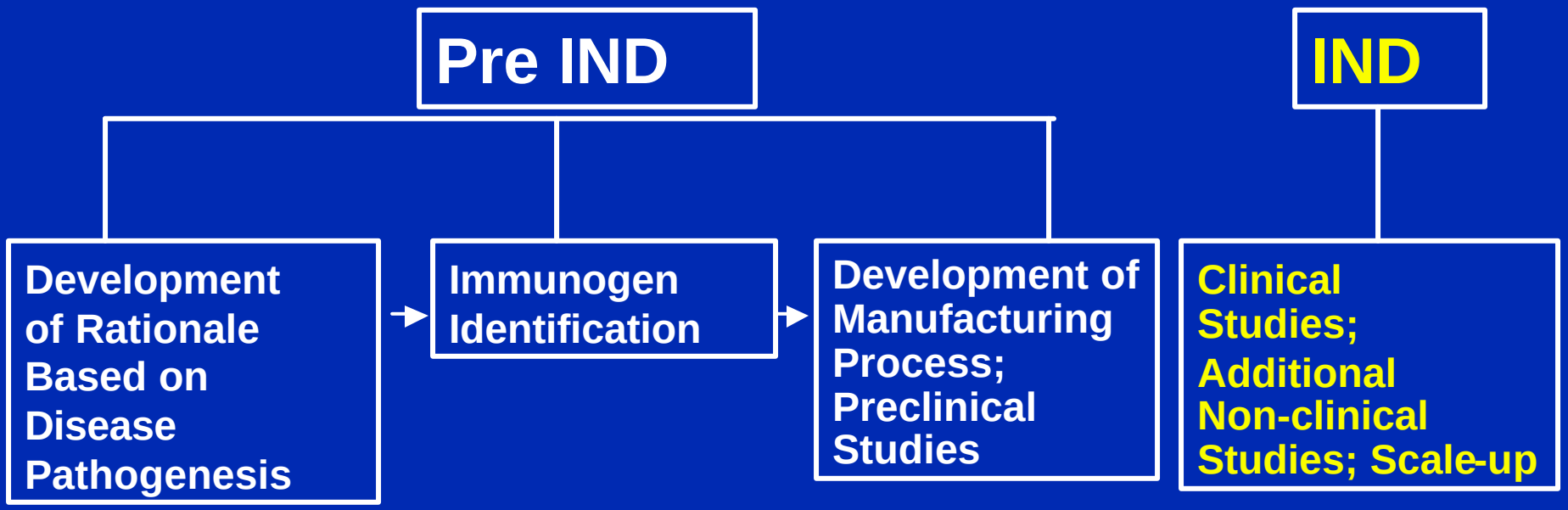
21 Code of Federal Regulations (CFR):

Part 600-680	Biologics
Part 312	INDs
Part 201, 202	Labeling and advertising
Part 210, 211	cGMPs
Part 800	*in vitro* diagnostics
Part 25	Envir. Assessments
Part 50	Informed Consent
Part 54	Financial disclosure
Part 56	Institutional Review Boards
Part 58	GLP-Nonclinical Lab Studies

Regulatory Definitions

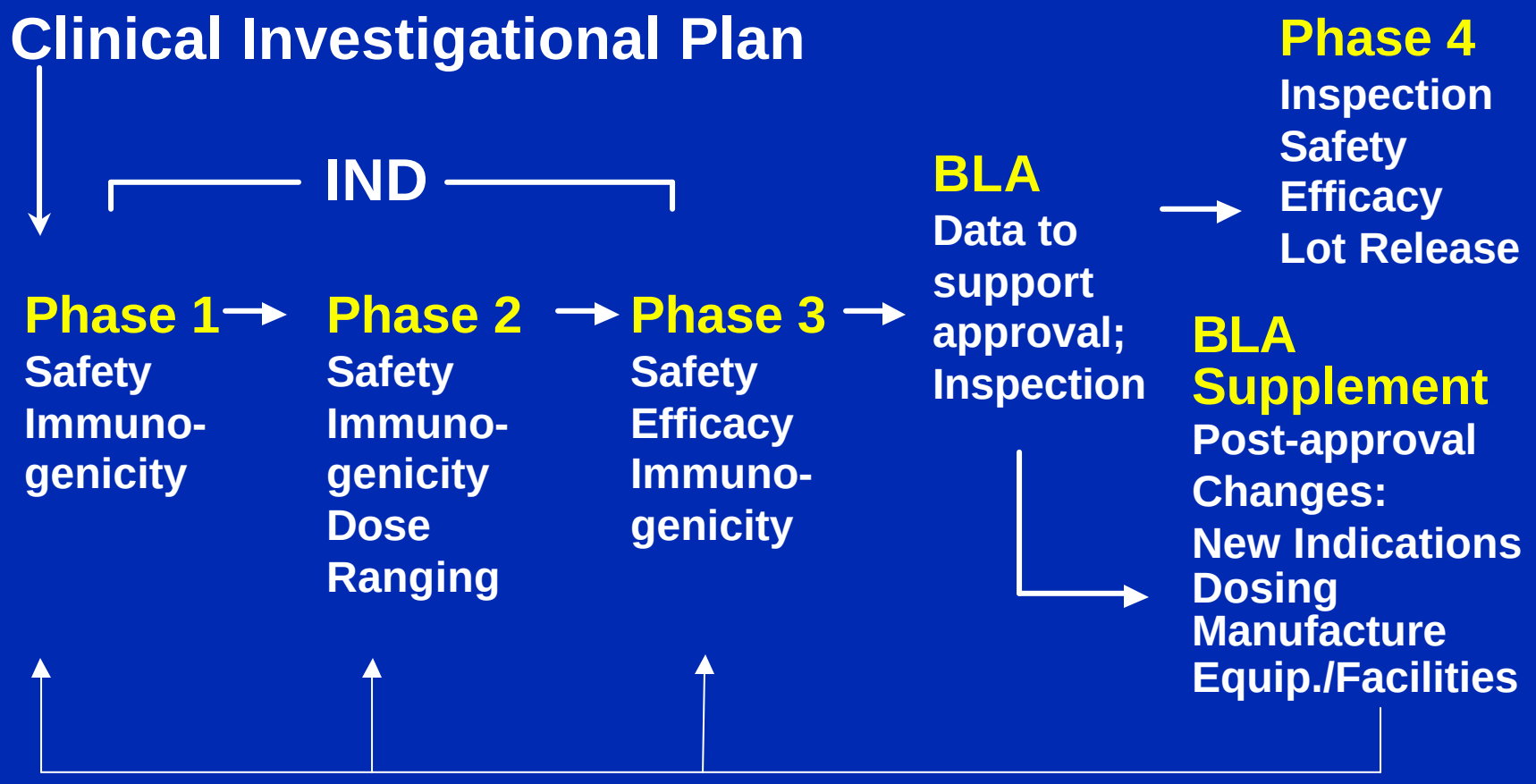
- Safety (21 CFR 600.3)
  - ✓ Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...
- Purity (21 CFR 600.3)
  - ✓ Relative freedom from extraneous matter in the finished product...
- Potency (21 CFR 600.3)
  - ✓ Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Vaccine Development



IND = Investigational New Drug application

Stages of Review and Regulation



IND =Investigational New Drug Application; BLA=Biologics License Application

Review of Investigational New Drug (IND) Applications

Product Jurisdiction (21 CFR Part 3)

- Primary mode of action
- Informal assistance
- Inter-center agreements
- Inter-office agreements
- Request for Designation (RFD)
- Center or FDA Ombudsman
- Office of Combination Products

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Typical IND Review Team

- Primary Regulatory Reviewer
- Product Reviewer (s)
- Clinical Reviewer (Physician)
- Pharm/Tox Reviewer
- Statistician
- Other specialty consult reviews as needed

General Principles

"FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, … FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations…, [21 CFR, 312.22(a)]

General Principles

- “…and in Phase 2 and 3, to help assure that the <u>quality of the scientific evaluation of drugs is adequate</u> to permit an evaluation of the drug’s effectiveness and safety….” [21 CFR, 312.22(a)]

Meetings with FDA (21 CFR 312.47, FDAMA, CBER guidance)

Phase 1 → Phase 2 → Phase 3 → License Application

Pre-IND Meeting:
Rationale
Manufacturing
Product
Lot Release
Animal safety & immunogenicity
Phase 1 protocol

End-of-Phase 2 Meeting:
Efficacy trial protocol(s)
Phase 1/2 data
Update Product,etc.
Assay validation (potency, immun.)

Pre-BLA Meeting:
Clinical data summary: S & E
Update: Product, etc.
Outline of BLA

IND Content & Format (21 CFR 312.23)

- Cover sheet (Form 1571)
- Table of contents
- Introductory statement & general investigational plan
- Investigator’s brochure
- Clinical protocol

IND Content & Format (21 CFR 312.23)

- Chemistry, manufacturing, & control information
- Labeling (invest. use only)
- Pharmacology & toxicology information
- Previous human experience
- Additional information

Clinical Protocol Elements 21 CFR 312.23 (a)(6)(iii)

- Objectives & purpose
- Investigator info (Form 1572, CV)
- Inclusion/exclusion/# of subjects)
- Study design
- Dose & schedule
- Monitoring to meet objectives
- Monitoring to minimize risks

Clinical Holds

- Regulation: 21 CFR 312.40
  - ✓ Study may proceed after the 30 day review period unless sponsor is notified otherwise by FDA
- Clinical Hold (21 CFR 312.42):
  - ✓ Order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation

Clinical Holds

- Grounds:
  - ✓ Phase 1:
    - Unreasonable & significant risk
    - Clinical investigators not qualified
    - Inadequate investigator's brochure
    - Insufficient information to assess risk

Clinical Holds

A clinical hold on your Phase 1 study can frequently be avoided by requesting a pre-IND meeting well in advance of submission of the IND.

We will work with you!

Clinical Holds

- Grounds:
  - ✓ Phase 2/3:
    - Same reasons for Phase 1
    - Protocol design inadequate to meet objectives

Clinical Holds

- Notification:
  - ✓By telephone or fax
- Clinical hold letter:
  - ✓Within 30 calendar days of hold notification
- Additional comments (Non-Hold) Letter
- Review of complete hold response
  - ✓Within 30 days of receipt of response

IND Amendments (21 CFR 312.30 – 312.33)

- Protocol amendments:
  - ✓Existing protocol
  - ✓New protocol
- Information amendments (e.g., product changes)
- Safety reports
- Annual reports

An IND can be placed on clinical hold at any time for safety reasons (all Phases) and/or for clinical design issues for Phase 2 or 3 studies.

Vaccine IND Submissions: Common Pitfalls

- Administrative
- Manufacturing
- Lot Information
- Preclinical Issues
- Protocol Issues

Vaccine IND Submissions: Common Pitfalls

- Administrative
  - ✓ At least 3 copies of submission
  - ✓ Completed & signed Form 1571
  - ✓ Specific cross-references (IND/MF, date, volume number, page)
  - ✓ Pages numbered sequentially
  - ✓ Clear images of gels & blots

Vaccine IND Submissions: Common Pitfalls

- Manufacturing
  - ✓Insufficient information
  - ✓Variable conditions
  - ✓Lot release test results lacking
  - ✓Potentially toxic substances - validation of removal or assay for residual component

Vaccine IND Submissions: Common Pitfalls

- Manufacturing
  - ✓ Adventitious agents - inadequate testing or inadequate information on source materials

Vaccine IND Submissions: Common Pitfalls

- **Preclinical Issues:**
  - ✓ **Pyrogenicity**
  - ✓ **Attenuation (live organisms)**
  - ✓ **Inactivation/reversion**
  - ✓ **Immunogenicity (potency) data lacking**
  - ✓ **GLP safety study (Phase 1)**

Vaccine IND Submissions: Common Pitfalls

- ✓ Experimental details lacking
  - Need information on lot, dose, route, assays to evaluate immune response
- ✓ Support dose proposed for clinical trial

Vaccine IND Submissions: Common Pitfalls

- **Protocol Issues:**
  - ✓ Include subject diary card and case report form to monitor reactogenicity
  - ✓ Describe assays to evaluate immune response
  - ✓ Define end point(s) & case definition
  - ✓ Describe statistical analyses
  - ✓ Inconsistencies

Available CBER Guidance

- Guidance for Industry
- Guidelines
- Points to Consider
- Federal Register Notices
- ICH Topics & Guidelines
- Reviewers' Guides
- CBER SOPP

CBER Guidance

- Web: www.fda.gov/cber/reading.htm
- Email: OCTMA@CBER.FDA.GOV
- Fax: 1-888-CBER-FAX
- Phone
  - ✓ DVRPA: 301- 827-3070
  - ✓ OCTMA: 301- 827- 1800

Summary

- Product Dev: A Continuous Process from Pre-IND to Post-marketing
- Interaction with CBER: Early and Throughout the Process
- IND Format and Review: Data Driven Process
- Continuum Approach: Sliding Scale of Requirements from Phase I to Phase III

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