Regulatory Considerations for the Manufacture of Investigational Vaccines for Clinical Trials

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Office of Vaccines Research and Review

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Topics to be Covered

- Role of OVRR in the regulation of vaccines and related products
- Vaccine manufacture & characterization (general)
- Vaccine manufacture & characterization (type-specific)
- Role of assays in vaccine development
- Summary & available resources

Regulation: What is the value added?

- Need for consistent and objective protection of the public's safety and need for trust
- Public expects safe and effective products, especially vaccines given to well individuals
- Preserving confidence in medical products and public health leadership is critical

FDA Review is Product-based

- Parallels prudent product development
- Dependent on characteristics of specific product
- Preclinical studies designed to support use of specific products
- Clinical trial design supported by manufacturing & preclinical data
- Supported by science, framed by regulations

Vaccine Development

- The development of a vaccine is a complex process resulting in the licensure and commercialization of a product that has been demonstrated to be safe and effective and that can be manufactured in a consistent manner.
- The FDA is committed to fostering the efficient, rapid development of vaccines needed for the public health.

CBER's Office of Vaccines Research & Review

- Consists of ~300 regulatory and scientific staff
- One application division and three laboratory divisions
- Mission is to assure the purity, potency, safety, and efficacy of vaccines and related biological products
  - Preventive vaccines
  - Therapeutic vaccines for infectious disease indications
  - Toxins & allergenic products

Manufacturing and Product Quality Activities

- Enhance risk-based oversight and quality of manufacturing throughout product life cycle
- Continued training and outreach on vaccine quality and cGMPs
- Continued efforts to modernize and where possible to harmonize with other regulatory authorities (PIC/S)
- Risk-based compliance programs
  - Evaluate existing programs and expand to new areas

Manufacturing and Product Quality Activities

- New CBER laboratories in newly created Division of Product Quality
  - Quality environment for critical product testing and standards activities
  - Ongoing efforts toward ISO certification
- Research to modernize approaches
  - Develop/evaluate more rapid potency and other lot release and product characterization assays
  - Enhanced methods to measure immune responses

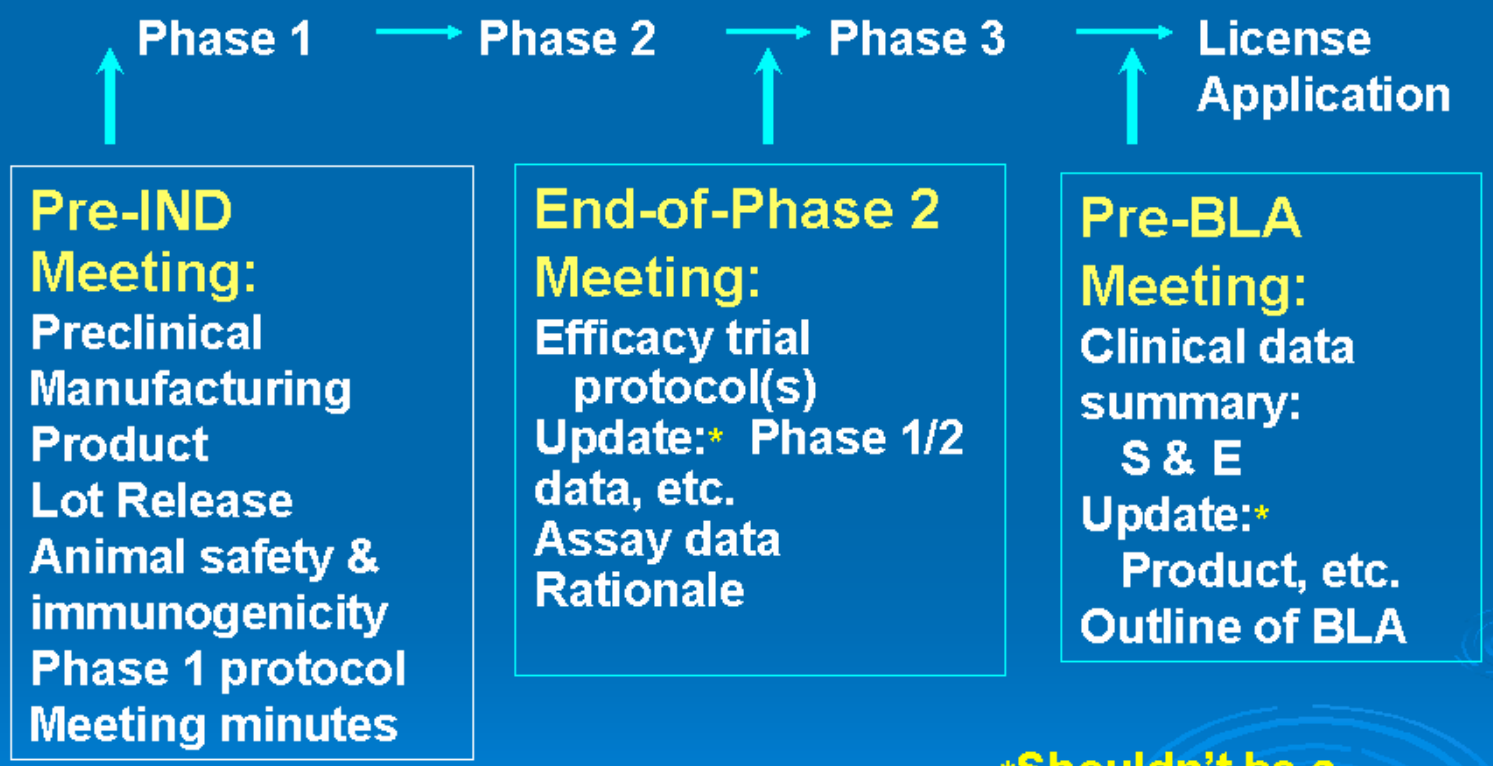
IND Role in Biologics Approval Process

- Mechanism and process to collect clinical data to support the license application
  - Demonstrate safety and efficacy
  - Goal: Information for the package insert
- Chemistry, manufacturing, and controls (CMC)
  - General biological product standards
  - Process validation
- Assay validation
  - Immunogenicity/activity
  - Product quality control, lot release
- Stability data

Typical OVRR IND Review Team

- Regulatory Reviewer (Primary Reviewer)
- Clinical/Medical Officer
- Product Reviewer(s)
- Statistician
- Pharm/Tox Reviewer
- Others, as needed (e.g., cell substrate, assay validation, facilities)
- May need additional contact with CBER facilities staff (DMPQ/OCBQ/CBER)

Recommended Meetings with FDA



IND =Investigational New Drug Application
BLA =Biologics License Application

*Shouldn't be a surprise (e.g., pivotal data not seen previously)

Vaccine Manufacture & Characterization (General)

Licensed biological products, including vaccines, must be:

- **Safe:** "relatively free from harmful effect… when prudently administered, taking into account the character of the product in relation to the condition of the recipient at the time."
- **Pure:** "relatively free from extraneous matter in the finished product,…"
- **Potent:** "specific ability of the product … to effect a given result."
- **Manufactured consistently** according to current Good Manufacturing Practices

CGMP & Product Development

SAFETY INFORMATION

Source characterization

Raw materials qual

DS/DP Characterization

Testing/Qualification/ Clearance of impurities, contaminants

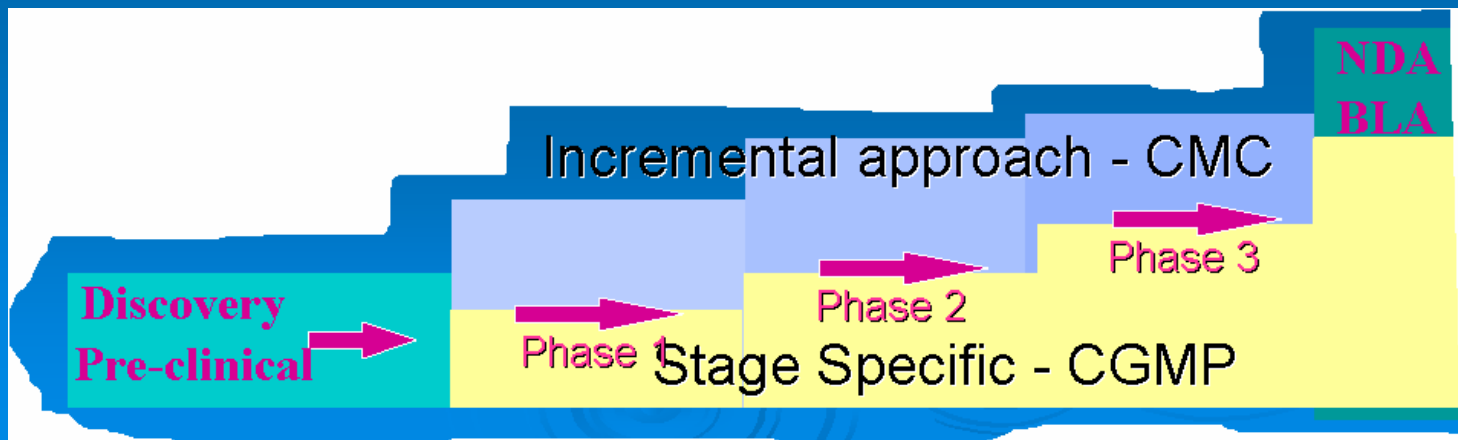
Process control esp. for safety processes (e.g., sterilization, virus clearance)

DEVELOPMENT ACTIVITIES

DS & DP Characterization
Formulation Development
Raw Material/ Component characterization
Assay Development/ Validation
Specification Development
Stability
Manufacturing Process Control & Validation

CGMP

Personnel
Quality Control
Facilities & Equipment
Laboratory Control
Component Control
Production Control
Distribution & Records
Labeling



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

IND Submissions - Common Pitfalls: Lot Information

- Lots not clearly identified
- Test results not submitted
- 21 CFR 312.23(a)(7)(i): assure proper identification, quality, purity and strength
- 21 CFR 610: potency, general safety, sterility, purity, identity
- Summary table - stage of manufacture, test, acceptance criteria, test result, data attached

Lot Release Testing

- Sterility – bacterial or fungal contaminants
- General safety test - guinea pigs and mice to detect extraneous toxic contaminants
- Identity test - e.g., SDS-PAGE, Western blot, immunologic assay or amino acid analysis
- Purity - e.g., % moisture, SDS-PAGE, HPLC, endotoxin
- Potency - *in vivo* or *in vitro* test to assess immunogenicity, antigen content, or chemical composition
- Tests for removal of process contaminants

Stability

- Defines product shelf-life (1 – 2 yrs)
- Stable product needed for clinical trials
- Establish program to evaluate stability at specific time intervals
  - Potency
  - Moisture
  - Sterility

Vaccine Manufacture & Characterization (Type-Specific)

Vaccine Types to be Discussed

- Plasmid DNA vaccines
- Live, Attenuated vaccines
- Vectored vaccines
- Vaccines delivered via device

DNA Vaccines - Manufacture

- Process development and QC issues
  - Cell origin, genotype & phenotype
  - Genetic stability (WCB)
  - Source of process components
  - Process contaminants in final product
  - Adventitious agents (e.g., bacteriophage) in MCB & WCB
- Genetic characterization
  - Verify DNA sequence of entire vaccine (vector plus insert) present in MCB
  - Changes to insert gene or vector sequences
    - - additional preclinical studies or a new IND may be required

DNA Vaccines - Safety

- Local reactogenicity & systemic toxicity
- Nature of the immune response
- Tissue localization, persistence & integration
- Challenge/protection studies (demonstrate rationale for vaccine use)
- Prime/boost studies (support dose, schedule, route of each component)
- Cytokine expression (immunomodulation)

DNA Vaccines - Integration

- Potential Consequences of:
  - Genome instability
  - Inactivation of specific genes (tumor suppressors)
  - Activation of dominant oncogenes by insertion of promoters/enhancers
  - Germline alteration
- Biodistribution - if no signal (plasmid <30,000 copies per µg host DNA) is detected at study termination (typically Day 60), an integration study is not required

DNA Vaccines - Integration

- **Biodistribution studies might be waived for DNA vaccines:**
  - **When a novel, but related, gene is inserted into a plasmid vector previously documented to have an acceptable biodistribution/integration profile**
  - **If minor changes are made to the vector**

Live Attenuated & Vectored Vaccines

- Characterization of cell banks – draft guidance at http://www.fda.gov/cber/gdlns/vaccsubstrates.htm
- Contaminants (e.g., host cell proteins)
- Level of attenuation/reversion
- Neurovirulence or Tumorigenicity (some viruses)
- Adventitious agents (e.g., viral, mycoplasma)

Live Attenuated & Vectored Vaccines

- Dose & route of administration
- Immune status
- Person to person spread (shedding)
- Colonization & ease of elimination
- Survivability in environment

Vectored Vaccines

- Construct characterization
- Persistence of expression *in vivo*
- Safety of extended antigen expression (e.g., BCG vectors)
- Potency
- Transfer of antibiotic resistance
- Combination vaccine?

Vaccines Delivered Via Device

- Antigen dose/persistence
- Antigen delivery (bioavailability)
  - Substrate inertness
  - Antigen adsorption
- Vaccine denaturation
    - Molecular shearing/viscosity changes
- Contamination
- Cross-contamination of patients with disease agents

Assays in Vaccine Development

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Importance of Assays:

- To assess product quality, e.g., potency
- To detect vaccine-elicited immune response(s)
- To assess efficacy endpoints, e.g. define a disease case prevented by the vaccine
- To assess interference with concomitant vaccines (e.g., pediatric vaccines)
- Functional antibody assays (e.g., opsonophagocytic) may be needed in addition to binding alone (e.g., ELISA)
- Considerable R & D may be necessary

Assays in Vaccine Trials

- Assay performance data
  - Specificity, sensitivity, ruggedness, reproducibility, e.g., procedures to minimize false positive PCR
  - Important for early trials
  - Critical for pivotal trials, e.g., efficacy trials (assay validation is critical)
- Typical results reported & analyzed as
  - Percent responders
  - Geometric Mean Titers (GMT)

Summary

- Licensed vaccines must be:
  - Safe and effective
  - Manufactured consistently under cGMP, consistent with the stage of development
  - Vaccine testing encompasses:
    - Product characterization
    - In process, lot release, and stability
- Assays are important!

Summary

- FDA facilitates development, licensure, and availability of new vaccines through
  - New Guidance
  - New assays and standards to evaluate safety, potency, quality
- Ongoing communication with FDA is critical

Available Resources

- Finn TM, Egan W: Vaccine Additives and Manufacturing Residuals in United States-Licensed Vaccines. Vaccines, 4th ed., 2004, WB Saunders
- Shapiro SZ: The HIV/AIDS Vaccine Researchers' Orientation to the Process of Preparing a U.S. FDA Application …Preparing for Your Pre-IND Meeting. 2002, *Vaccine* 20:1261-80
- Chandler D, McVittie L, Novak J: IND Submissions for Vaccines. Vaccines: From Concept to Clinic, 1999, CRC Press

Available Resources

- FDA guidance documents, Federal Register notices, FDA regulations
- Guidance for Industry: Content and Format of Chemistry, Manufacturing and Control Information and Establishment Description Information for a Vaccine or Related Product, 1999
- International Conference on Harmonisation (ICH) documents (U.S., E.U. and Japan)
- Baylor NW, Midthun K: Regulation & Testing of Vaccines. Vaccines, 4th ed., 2004, WB Saunders

Available Resources

- **Web:**
  www.fda.gov/cber/vaccine/vacpubs.htm
  www.fda.gov/cder/guidance/index.htm
- **Email: MATT@CBER.FDA.GOV**
- **Phone: 301-827-1800 or 800-835-4709**

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