Vaccine Development and Licensure Pathways: An Emerging Infectious Disease Vaccine Example

Fall CMC Strategy Forum

October 13, 2020

Robin Levis, Ph.D.

Division of Viral Products

Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

Overview

General considerations for vaccines

- Pre-licensure development
- Approval pathways
- Pathways to expedite review and licensure

Development of vaccines against emerging infectious diseases

- Lessons learned from Ebola virus vaccine development during public health emergency
- Applicability of lessons learned to support the accelerated development of vaccines against other emerging infectious diseases
  - Notes on SARS-CoV-2 vaccine development

Vaccine Development against Emerging Infectious Diseases

- Follows same paradigm as other preventive vaccines
  - Unique considerations if development occurs in a public health emergency
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Product-related data and testing plans adequate to support the manufacturing process in an appropriate facility, characterize stability, and ensure consistency of manufacture
  - Pre-clinical data: supportive of initiating clinical studies
  - Human clinical data adequate to support the proposed indication and use
  - Facility data: compliance w/cGMPs, manufacturing controls, QA/QC
  - Post-licensure pharmacovigilance plan

Development Goals Under IND

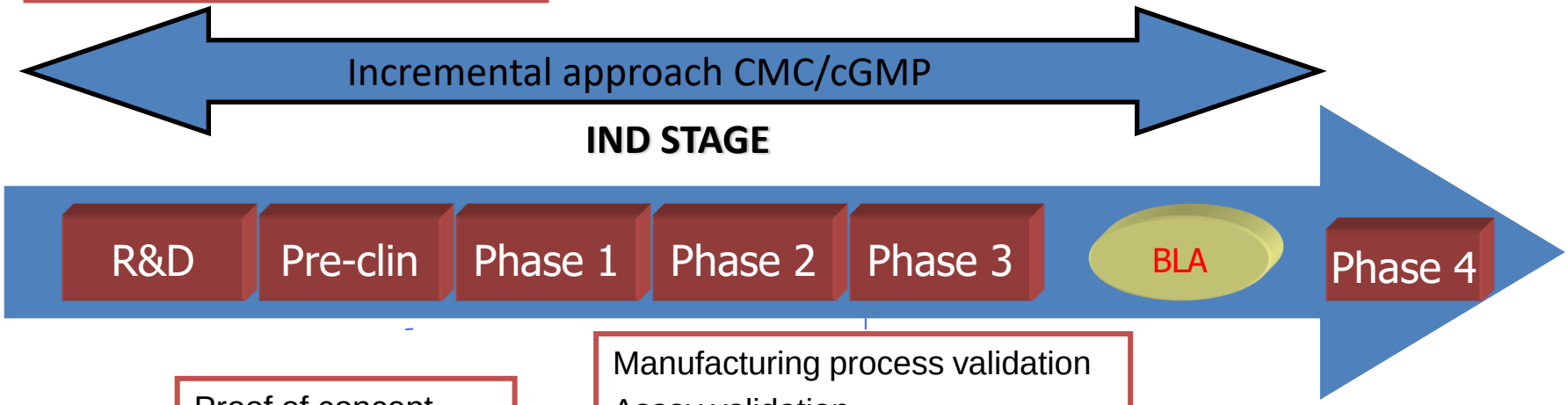
- CMC – Phases 1 and 2
  - Define and qualify the manufacturing processes
  - Evaluate consistency and quality of the product with regard to composition and safety
- CMC – Phase 3
  - Demonstrate manufacturing consistency
    - Identify CPPs and validate process
    - Qualification of facilities
  - Quality control
    - Validation of all assays used to support product quality
      - Establish specifications
      - In process and final container

Vaccine Development - Overview

Process Development
- Source characterization
- Raw material qualification
- Cell bank characterization
- DS/DP characterization
- Assay development
- Formulation development
- Process controls

Process Optimization
- In-process controls
- DS/DP characterization
- Formulation optimization
- Assay qualification
- Specification development
- Stability

BLA Supplement:
- Manufacturing changes
- Formulation changes



Proof of concept
Pre-clinical safety

Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

Licensure Pathways

- Traditional Approval
- Accelerated Approval*
- Animal Rule Approval*

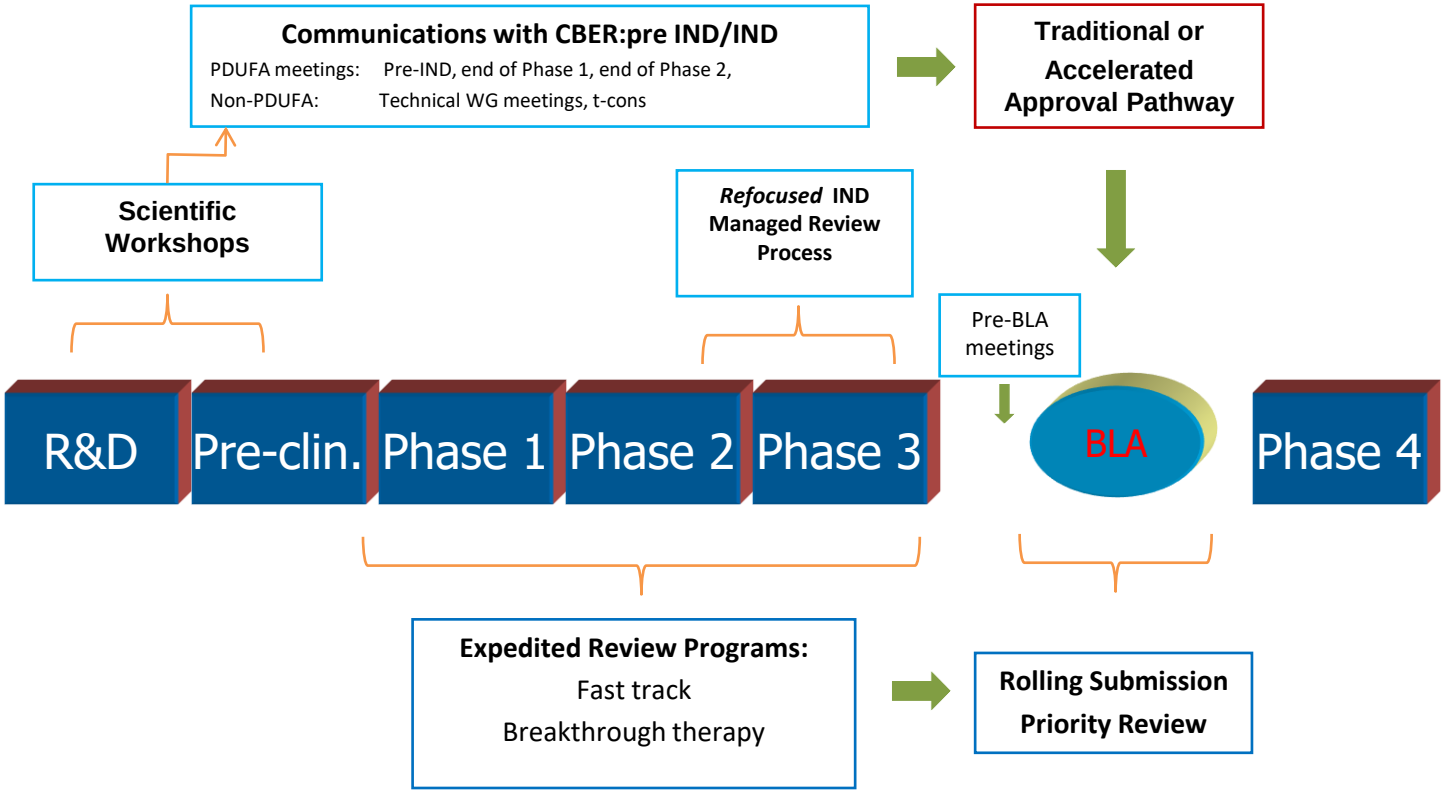
Demonstration of clinical safety required for all pathways

Demonstration of effectiveness required for all pathways; differences in approach among pathways

Demonstration of manufacturing consistency and product quality required for all pathways

**Accelerated Approval and Animal Rule-- specific "eligibility" criteria and associated requirements*

Strategies for Accelerating Vaccine Approval



Facilitating the Development of Vaccines for Emerging Infectious Diseases:

Lessons from Ebola Vaccine Development

Facilitating Ebola Vaccine Development - Role of FDA

When confronted with an emerging disease with significant public health impact:

- FDA provided expedited review of chemistry, manufacturing and controls (CMC) information, preclinical and clinical protocols, and clinical trials data, where available
- Numerous meetings with sponsors to discuss CMC issues, clinical development programs, and pathways to licensure for Ebola virus vaccines

Facilitating Ebola Vaccine Development - Role of FDA (cont.)

- International collaboration among regulatory agencies in review, with goal of regulatory convergence
- Participation in WHO organized joint reviews with African regulators
- Scientific workshop (Dec 2014) on Ebola virus and vaccine immunology
- FDA Vaccines Advisory Committee public meeting (May 2015) to discuss clinical development of Ebola vaccine candidates

Key Considerations for Ebola Vaccines

- Vaccine approval is based on validated and well-controlled manufacturing process
- Vaccine approval is based on adequate and well-controlled studies demonstrating safety and effectiveness
- Ebola vaccines might be licensed based on
  - Clinical benefit
    - Disease endpoint efficacy studies;
    - Studies that show an effect on a surrogate marker (e.g., immune response) reasonably likely to predict clinical benefit; and/or
  - Animal studies
- The regulatory review of each vaccine will be data-driven and licensure pathways might differ

Clinical Trial Design Considerations for Ebola Vaccines

- Phase 1 and 2 studies to provide preliminary safety and immunogenicity data and to assess the optimal dose.
  - Larger phase 1 clinical studies to increase the early safety and immunogenicity database, facilitating timely initiation of Phase 2 clinical studies.
- Compressed timelines for clinical development, by initiating Phase 3 studies based on interim safety and immunogenicity data from earlier phase studies rather than on data from final study reports.
  - Disease epidemiology had major impact on the timing and design of Phase 3 studies.
- Randomized, controlled trials that have clinical disease as the endpoint are the most robust study designs for demonstrating vaccine efficacy
  - However, other study designs and approaches were found to be appropriate
- Close collaboration between public health authorities, national regulatory agencies, the community, clinical investigators, and vaccine developers was essential to ensure ethical conduct and that licensure requirements were met

Regulatory and Scientific Issues in Ebola Vaccine Development - Animal models

- Nonclinical studies: NHP models important to
  - Provide initial safety data to support phase 1 studies
  - Where applicable, the use of animal models can be important to understanding disease and mechanisms of protection
  - Support use of animal rule for licensure
  - However, vaccine doses that induce comparable immune responses may differ between humans and NHPs and may need additional studies in some cases

Regulatory and Scientific Issues in Ebola Vaccine Development - Assays

- Critical to evaluate serology samples derived from pivotal trials using validated assays
  - For both human and NHP studies
- Assays for case ascertainment and immune response
  - Comparability of data across studies desired
  - Review of study data from multiple potential sponsors with concurrent clinical studies
  - Review of study data from multiple studies done with a single product
  - Assay comparability, standardization, validation
    - Use of Master Files to facilitate information submission across multiple sponsors/products

Regulatory and Scientific Issues in Ebola Vaccine Development - CMC

- Product characterization and testing
  - Supportive data from platform-related products
  - Exceptions to testing of extraneous agents (viral pathogens, mycoplasmas)
    - Suitability and safety of product otherwise established (adventitious agent testing)
- Specifications for some assays based on related products (same vector backbone but different insert)
- Abbreviation of certain aspects of process validation
  - Supportive validation data from platform-related products
  - Full validation of critical assays
    - Justification for validation of non-critical assays after product approval
- Product use prior to availability of real time stability data, especially for early clinical trials

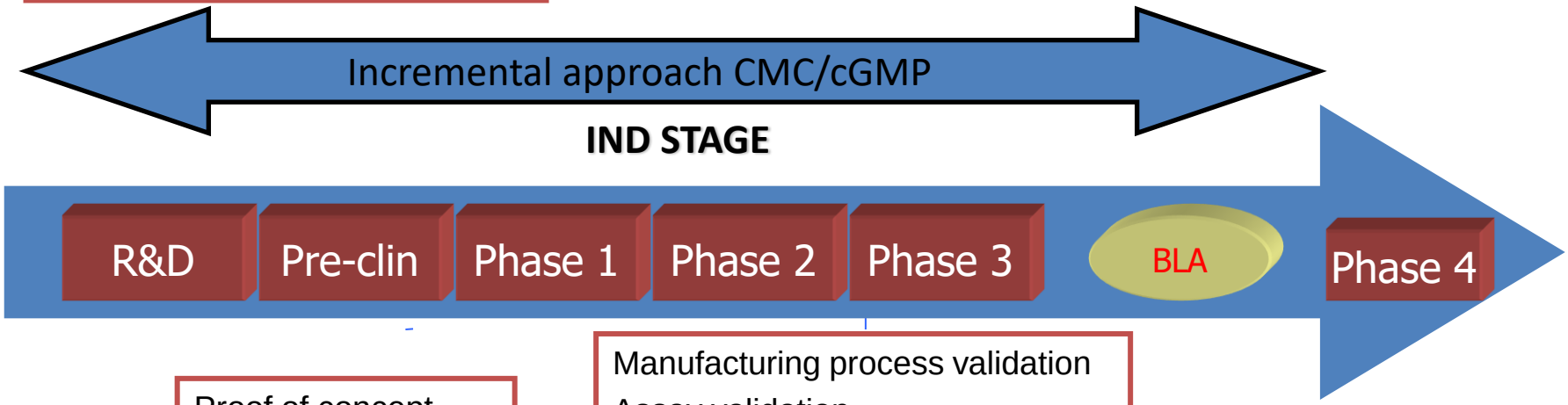
- Challenge was/is to keep pace with clinical development

Vaccine Development: Overview

Process Development
- Source characterization
- Raw material qualification
- Cell bank characterization
- DS/DP characterization
- Assay development
- Formulation development
- Process controls

Process Optimization
- In-process controls
- DS/DP characterization
- Formulation optimization
- Assay qualification
- Specification development
- Stability

BLA Supplement:
- Manufacturing changes
- Formulation changes



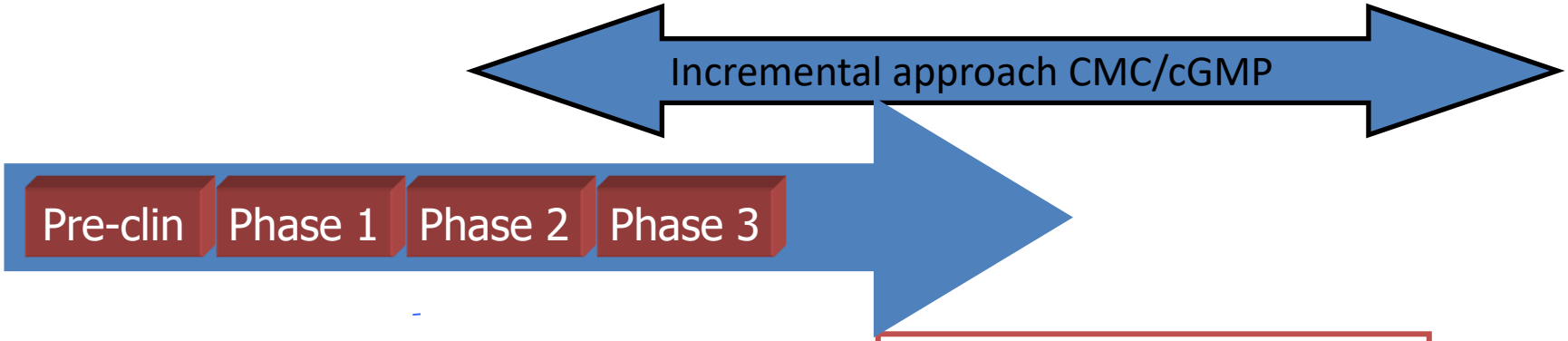
Proof of concept
Pre-clinical safety

Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

Ebola Vaccine Development Pathway Expedited Clinical Development

Process Development
- Source characterization
- Raw material qualification
- Cell bank characterization
- DS/DP characterization
- Assay development
- Formulation development
- Process controls

Process Optimization
- In-process controls
- DS/DP characterization
- Formulation optimization
- Assay qualification
- Specification development
- Stability



Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

Summary of Regulatory and Scientific Issues in Ebola Vaccine Development

- Multiple vaccine candidates
  - Parallel review of clinical studies studies for regulatory decision making
  - Communicating with different sponsors testing the same vaccines while maintaining confidentiality
  - Studies of a given vaccine may not be conducted under oversight of the same regulatory authority, yet their outcomes need to be considered in decision making
- Coordination of CMC and clinical development
- Pathways to licensure
- Postmarketing studies

Critical Considerations for Next-Generation Filovirus Vaccines

- In an outbreak scenario
  - Refer to previous slides!
- In the absence of an outbreak
  - Most likely animal rule approval will be considered
    - Critical to discuss clinical trial design with FDA
  - Continue efforts to develop and characterize animal models
    - Potentially more difficult with combination vaccines
  - Validate assays as early as possible
    - Critical for analyzing vaccine in animal model
    - Critical for bridging to human trial participants

Unique and Critical Considerations for SARS-CoV-2 Vaccines

- Global nature of the pandemic
  - Changes the risk benefit equation
- Expedite the expedited….
- No prior knowledge
  - Limited information from SARS and MERS
- Continue efforts to learn whatever we can about the virus, disease pathology, relevant immune responses, while we are manufacturing and testing vaccines in an accelerated fashion
- Establish minimum CMC, safety, clinical endpoints
- Use of EUA

COVID Vaccine Guidance

- Vaccine Guidance:
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

- EUA Guidance:
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19

Summary Remarks

- FDA approves vaccines based on data derived from adequate and well-controlled studies demonstrating the safety and effectiveness of the vaccines.
- Only those vaccines that are demonstrated to be safe and effective, and that can be manufactured in a consistent manner will be licensed by the FDA (or authorized for use under EUA)
- Vaccines against emerging infectious diseases could be licensed based on clinical endpoint efficacy studies, studies that show an effect on a marker *reasonably likely* to predict clinical benefit, or animal studies.
  - Licensure pathway is dependent on disease incidence and data available.

Summary Remarks (cont.)

- Immunological data collected in ongoing and planned studies will play an important role in vaccine evaluation and licensure
- Each disease and vaccine candidate has its own considerations
- Continued engagement with stakeholders, e.g., vaccine manufacturers, clinical trial sponsors, national and international partners is critical for successful CMC and clinical development and licensure of vaccines against emerging infectious diseases.