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

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FDA U.S. FOOD & DRUG ADMINISTRATION

Overview

General considerations

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

Development of vaccines against emerging infectious diseases

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

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

Primary Objectives of IND Review

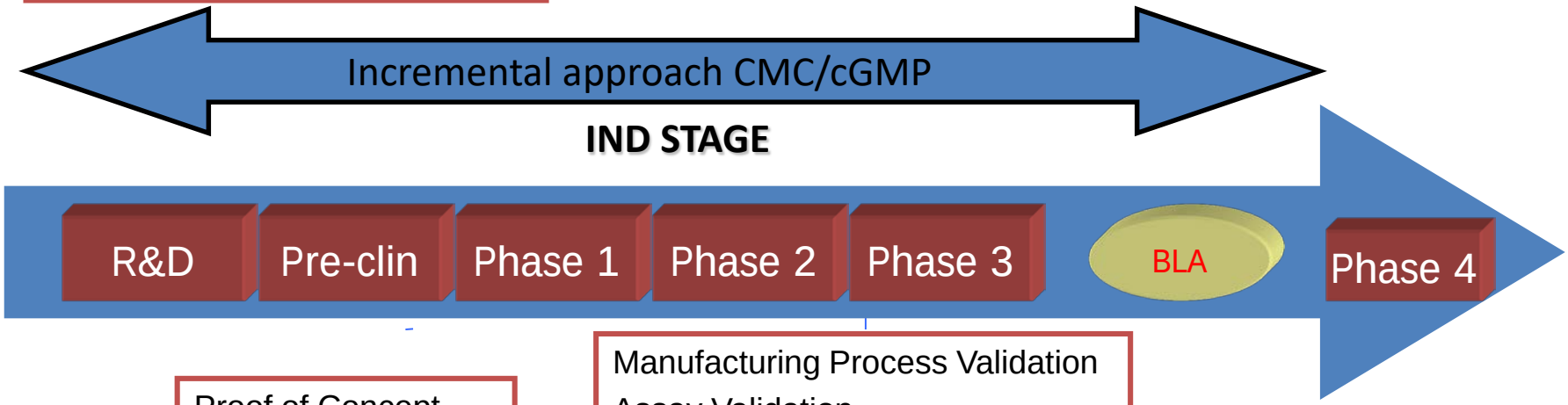
- CMC
  - Define, qualify, and validate manufacturing processes
  - Evaluate consistency and quality of the product with regard to composition and safety
- CMC – Phase 3
  - Demonstration of manufacturing consistency
    - Identification of CPPs and process validation
    - Qualification of facilities
  - Quality control
    - Validation of all assays used to support product quality
      - 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
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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*

Traditional Approval

Pre-licensure clinical studies provide evidence of effectiveness based on:

- Protection against clinical disease (not limited to serious or life-threatening disease)

- Immunologic response, in specific cases
  - Scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
  - Facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease

Accelerated Approval

- 21 CFR 601.40 and 601.41
- *Scope:* Products studied for safety and effectiveness in treating serious or life-threatening disease or condition AND that provide meaningful therapeutic benefit over existing treatments
- Approval may be based on adequate, well-controlled clinical trials establishing an effect on a surrogate endpoint that is **reasonably likely**…to predict clinical benefit…
- Requirement to verify clinical benefit; required postmarketing studies:
  - Usually underway at time of approval
  - Must be adequate and well-controlled
  - Must be conducted with due diligence

Animal Rule Approval

- 21 CFR 601.90-91
- For products for serious or life-threatening conditions when human efficacy trials are not ethical or feasible, *and approval based on other efficacy standards not possible*
  - Will rely on adequate and well-controlled studies in animals to provide evidence of effectiveness when well-characterized animal model(s) for predicting response in humans are available
  - Postmarketing studies to verify clinical benefit and to further assess safety required when such studies are feasible and ethical

Animal Rule Approval (cont'd)

Requirements to assure that animal studies establish reasonable likelihood of clinical benefit in humans,

- Pathophysiological mechanism of toxicity of the substance and prevention by the product well understood
- Effect shown in >1 species unless 1 model sufficiently well-characterized for predicting human response
- Animal endpoints clearly related to desired benefit in humans, generally improved survival or prevention of major morbidity
- Data allow selection of effective human dose

Requirement for postmarketing clinical studies to verify benefit and evaluate safety when such studies become ethical/feasible

Expediting Vaccine Development

- Fast track
- Breakthrough Therapy Designation
- Priority review
- Accelerated approval

These programs may be applicable for vaccines intended to prevent serious conditions

Fast Track

- Allows for more frequent communications with the FDA
  - Incorporates an end of Phase I meeting
- May allow for a “rolling” review of the BLA
- May allow for an accelerated approval of the product

Sec 506(b) FD&C Act, FDAMA of 1997, amended FDASIA 2012

Breakthrough Therapy Designation

- Treatment of serious or life threatening disease or condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies

- Benefit is increased interaction with FDA to expedite the development and review of the application

Sec 506(a) FD&C Act, added FDASIA 2012

Priority Review

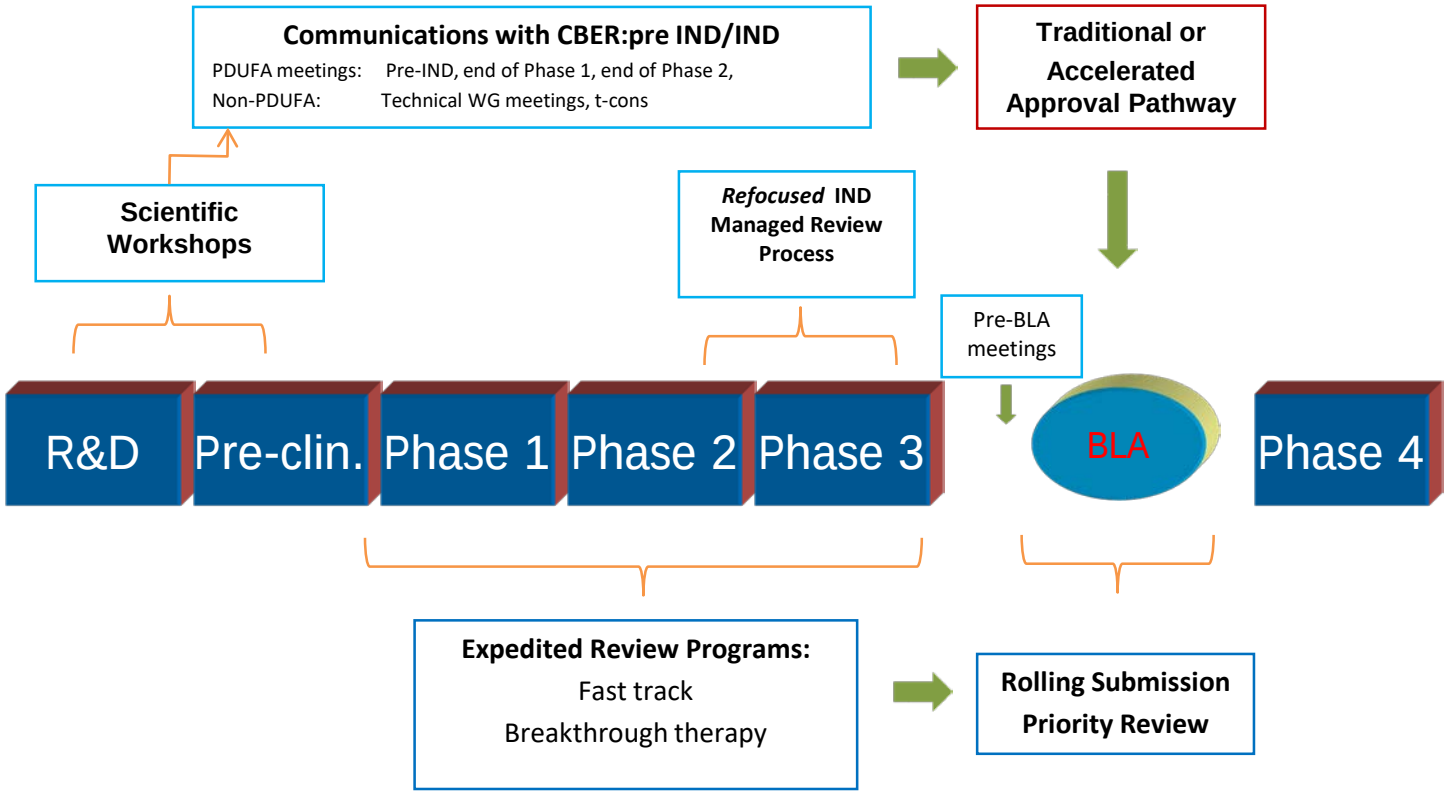
- Products regulated by CBER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a serious, life-threatening disease
- 6 months review of the entire BLA (instead of 10 months)
- A fast track product would ordinarily meet the criteria for a priority review (but not always)

Prescription Drug User Fee Act of 1992

Examples of expedited reviews

- Fast Track and priority– Prevnar 13 for unmet need of prevention of IPD caused by serotypes 1,3,5,6A,7F,19A which were not in Prevnar 7
- Fast Track and priority– Vaxchora cholera vaccine – first vaccine approved in US based exclusively on efficacy data from human challenge studies
- Fast Track and priority – Gardasil
- Fast Track but no priority review – Gardasil 9, Cervarix
- Breakthrough, priority review, and accelerated approval – Trumenba and Bexsero Meningococcal Group B vaccines
- Accelerated approval –Three new seasonal influenza vaccines.

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

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 to keep pace with clinical development

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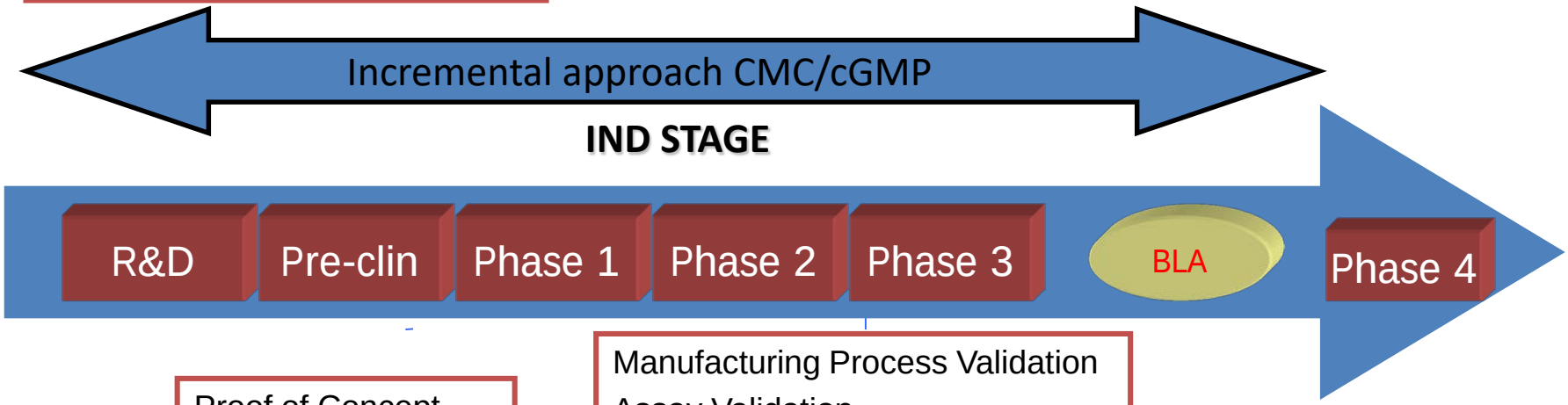

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Ebola Vaccine Development Pathway Expedited Clinical Development

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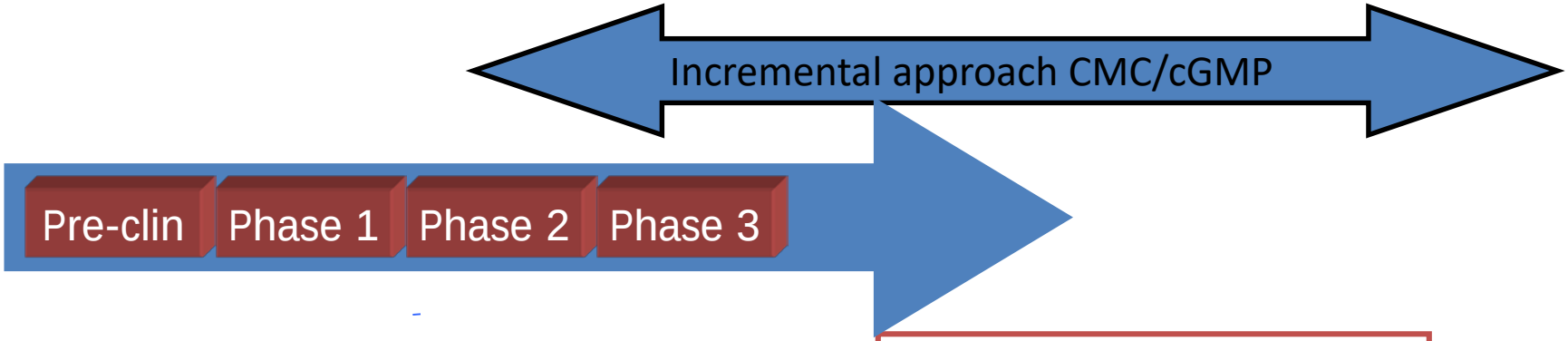

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Summary of Regulatory and Scientific Issues in Ebola Vaccine Development

- 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

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
- 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.
  - Approval under the accelerated or animal rule provisions would require postmarketing studies to verify/confirm clinical benefit of the vaccines

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.

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