Expedited Product Development: Application of Regulatory Lessons Learned

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FDA U.S. FOOD & DRUG ADMINISTRATION

Overview

General considerations for vaccines

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

Development of vaccines against emerging infectious diseases

- Early lessons learned from Ebola virus vaccine development during public health emergency
- Applicability of lessons learned to support the accelerated development of vaccines to prevent COVID-19
- What's next?

Vaccine Development against Emerging Infectious Diseases

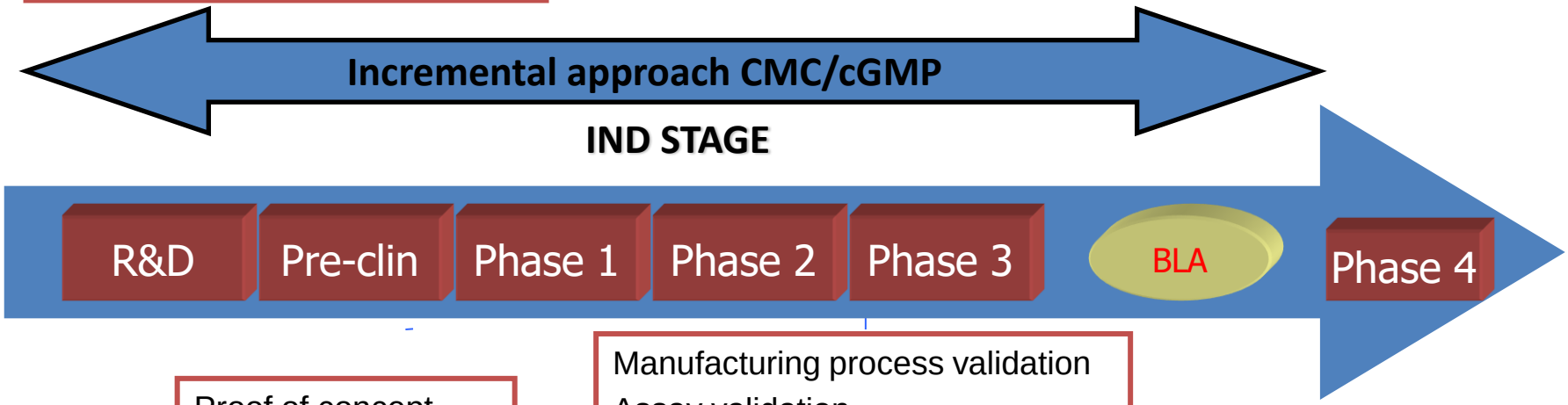
- Follows same paradigm as other preventive vaccines
  - Unique considerations if development occurs in a public health emergency
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Product-related data and testing plans adequate 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

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

Vaccine Development: Expedited Development Pathway - Ebola

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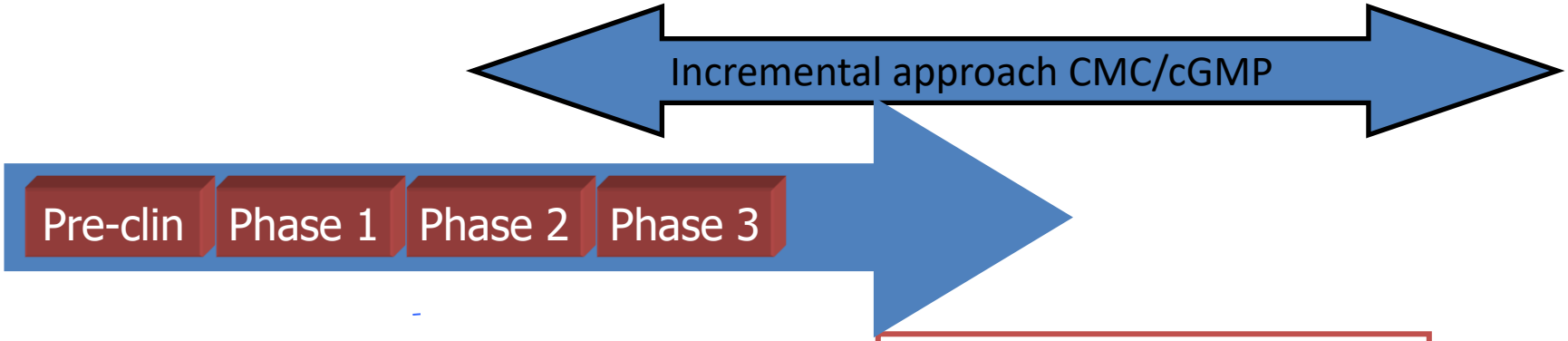

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Vaccine Development: Expedited Development Pathway - COVID

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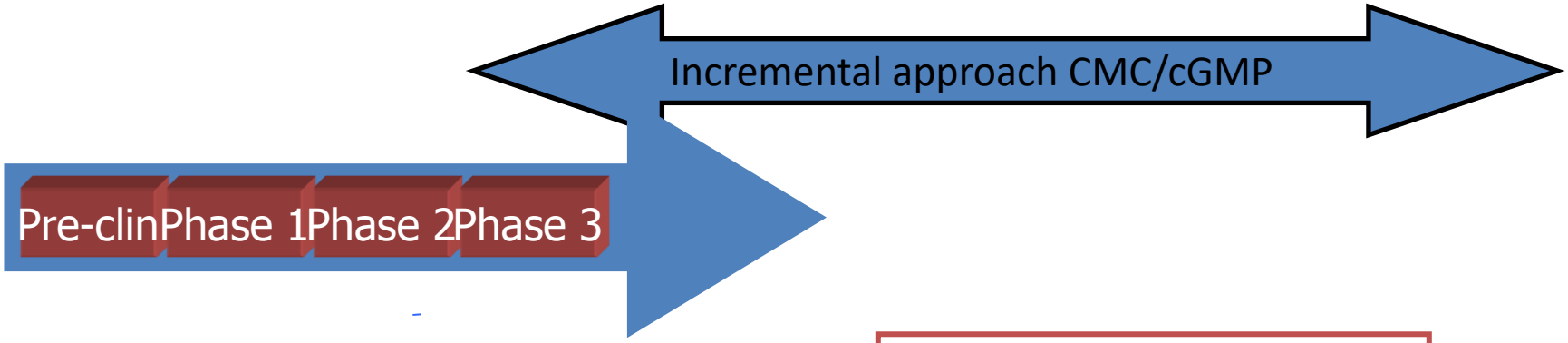

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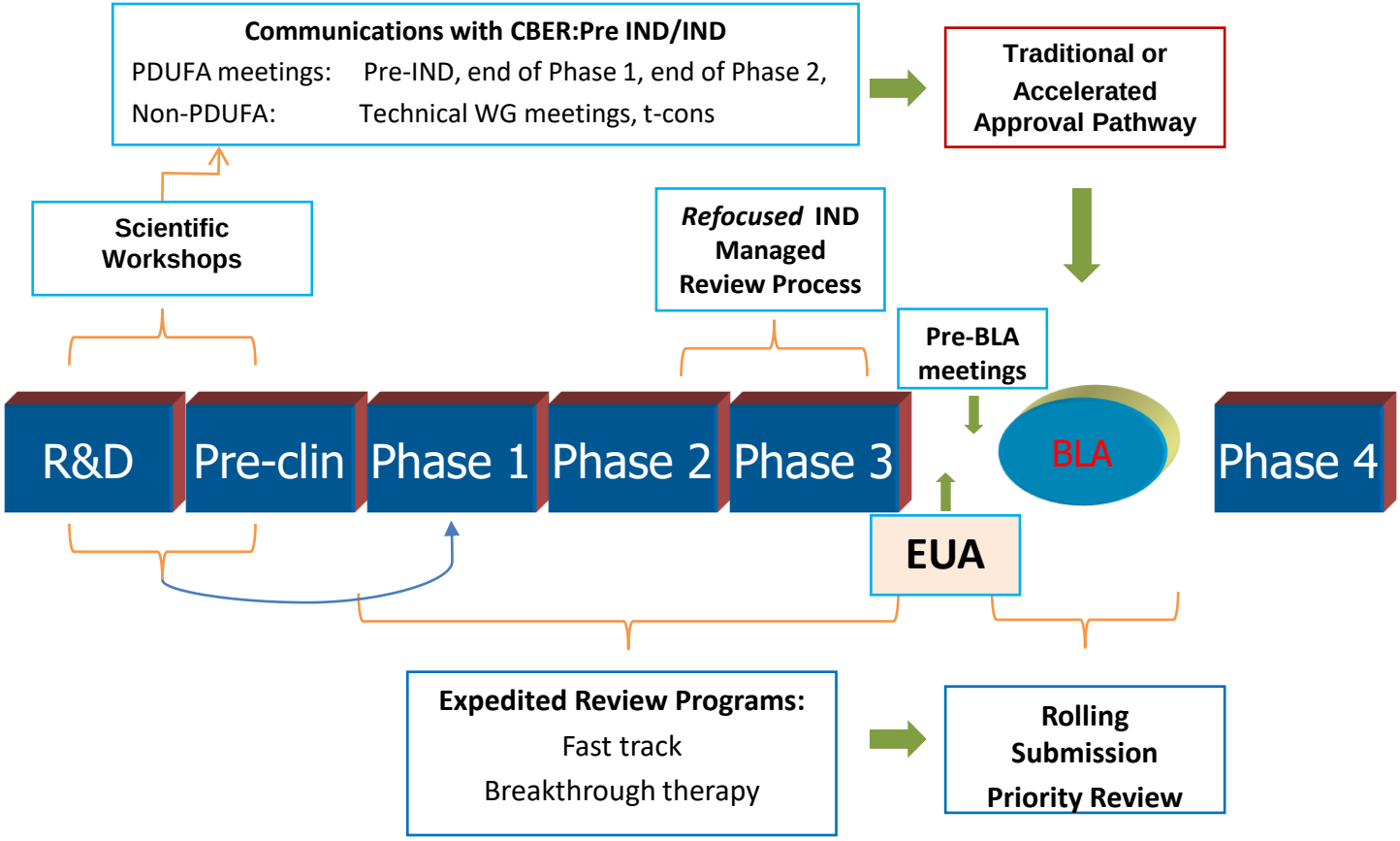
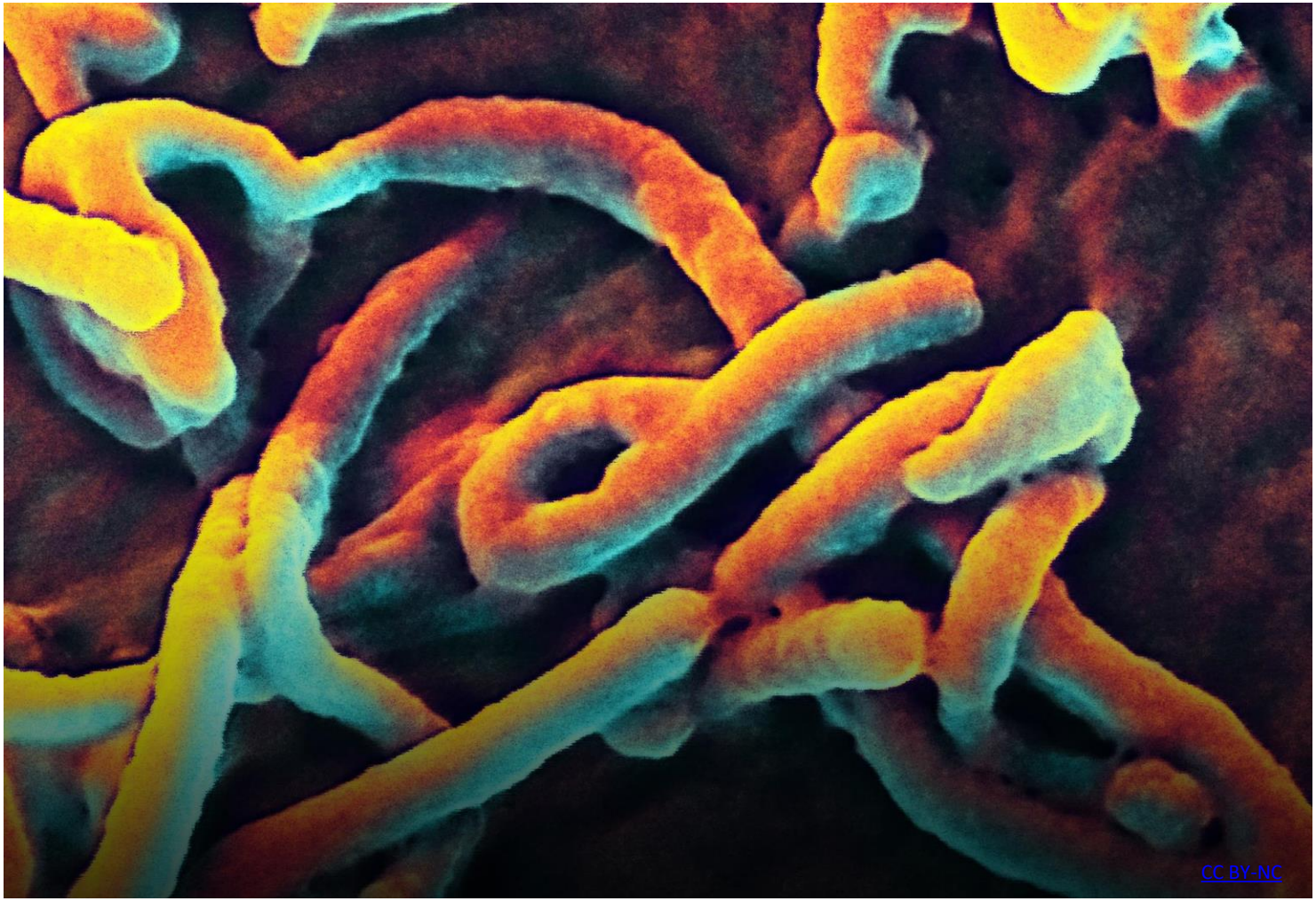
Strategies for Accelerating Vaccine Approval



Ebola Virus 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 was based on validated and well-controlled manufacturing process
- Vaccine approval was based on adequate and well-controlled studies demonstrating safety and effectiveness
- Future Ebola vaccines have been/may 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 was/will be data-driven

Regulatory and Scientific Issues in Ebola Vaccine Development - Animal models

- Nonclinical studies: NHP models important
  - 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

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 9 (for animal rule) 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)
- Initial 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

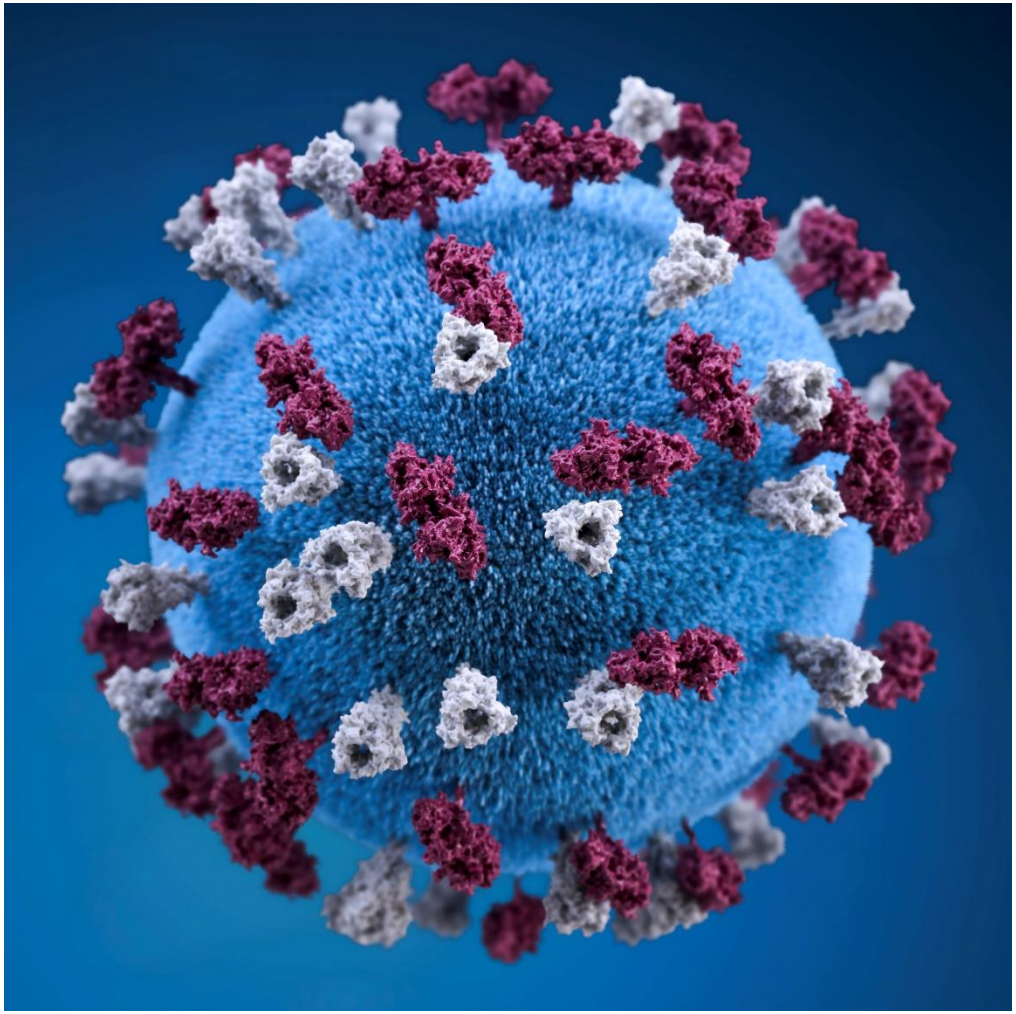
Regulatory and Scientific Issues in Ebola Vaccine Development – CMC (cont.)

- Based on need to work towards licensure as quickly as possible:
  - Sponsor agreed to submit the following CMC information post-licensure as supplements to the BLA:
    - Final stability results for the ongoing studies of the DP PPQ lots
    - Updated operating targets and ranges for the manufacturing process
    - Data to support the total processing time for the final DP process
    - Final drug product validation report
- In an outbreak setting, the challenge was/is to keep pace with clinical development

Summary of Regulatory and Scientific Issues in Ebola Vaccine Development

- Multiple vaccine candidates
  - Parallel review of clinical studies for regulatory decision making
  - Communicating with different sponsors testing the same vaccines
  - Studies of a given vaccine may not have been conducted under oversight of the same regulatory authority, yet their outcomes needed to be considered in decision making
- Coordination of CMC and clinical development
- Pathways to licensure
  - Animal rule vs. clinical efficacy

COVID-19 Vaccine Development



US Regulatory Framework to Make COVID-19 Vaccines Available

Licensure

Traditional Approval

Accelerated Approval

Animal Rule

IND

Unapproved product with no, or limited, human safety and effectiveness data

Expanded access use options

EUA

Unapproved product, or unapproved use of an approved product, in response to a public health emergency

Unique and Critical Considerations for COVID-19 Vaccines

- Global nature of the pandemic
  - Changes the risk benefit equation
- 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 and distributing vaccines
  - Emergence of variant virus strains
- Use of EUA

Considerations for COVID-19 Vaccines

- COVID-19 vaccines are being widely deployed and administered to millions/billions of individuals, at risk and healthy people
- Public expectation that COVID-19 vaccines will be safe and effective
  - Low tolerance for vaccine-associated risks
- Vaccine development can be expedited; however, there needs to be sufficient time to accrue adequate manufacturing (including facilities qualification), safety and effectiveness data to support potential widespread use of these vaccines
- Critical to continue global discussion and harmonization to facilitate rapid development, approval/authorization, and global distribution of vaccine
- **COVID-19 vaccines that are licensed in the US or authorized under EUA must meet applicable legal requirements**
  - **FDA will apply the same standards to grant a biologics license for a COVID-19 vaccine as for other preventive vaccines**

COVID-19 Vaccine Development and FDA Regulatory Activities – Lessons Applied

- **FDA must ensure that vaccines that are approved or authorized under EUA are supported by adequate scientific and clinical data**
- COVID-19 vaccine development may be accelerated based on knowledge gained from similar products and platform technologies
- Adaptive and/or seamless clinical trial designs allow for more rapid progression through the usual phases of clinical development
- FDA is facilitating COVID-19 vaccine development by
  - Providing expedited reviews of CMC and facilities information, preclinical and clinical protocols and clinical trials data
  - Providing timely advice and guidance to sponsors to expedite proceeding to Phase 3 clinical trials
  - Directing efforts at generating adequate data to support access to investigational COVID-19 vaccines
  - Directing efforts at generating adequate data to support full product licensure through BLA review

COVID-19 Vaccines: Development Strategy to Support EUA/Licensure

- Nonclinical data
  - Nonclinical safety studies – Rely on data from similar products using the same vaccine platform
  - Characterization of the immune response
  - Address the potential for vaccine-induced enhanced respiratory disease - Data required prior to Phase 1 study start
- Well defined manufacturing process to ensure product quality, consistency, and comparability across multiple facilities
- Product-related data and testing plans adequate to support the manufacturing process in an appropriate facility, to characterize stability, and to ensure consistency of manufacture
- Facility data to support product quality
  - Compliance with cGMPs
  - Quality systems in place

COVID-19 Vaccines: What's Next? - SARS-CoV-2 Variants of Concern

- Multiple SARS-CoV-2 variants have been identified
- Critical to establish impact of variants on vaccine efficacy
  - As well as other biologics used to diagnose or treat COVID-19
- Critical to establish pathway for the development and testing of vaccines against variants of concern
  - Non-clinical studies
  - Manufacturing and quality control
    - Product characterization
    - Potency
  - Clinical endpoints - immunogenicity
- Regulatory pathway to approve or authorize use of new vaccines

Where did we utilize "Lessons Learned"

- Relied on prior knowledge – case by case/platform by platform basis
  - Led to reduced nonclinical safety testing requirements
    - Toxicology studies and in some cases biodistribution studies
  - Use of platform related stability data to support clinical studies

- Product development and characterization in parallel with early phase clinical studies

- Enhanced engagement with stakeholders, e.g., vaccine manufacturers, clinical trial sponsors, national and international partners
  - Critical for global response
  - Harmonized response from regulators

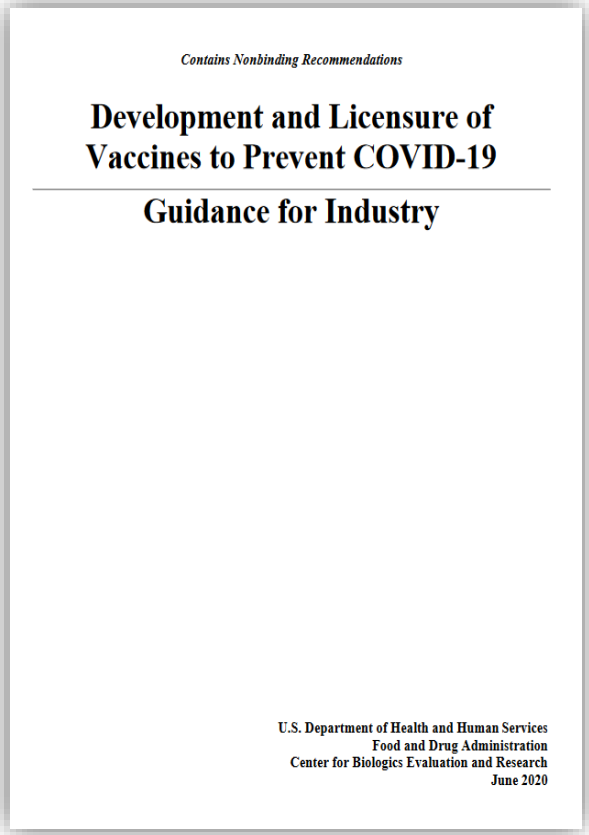
Where will we continue to utilize "Lessons Learned"

- Reliance on prior knowledge – case by case/platform by platform basis
  - Reduced nonclinical safety testing requirements
    - Toxicology studies and in some cases biodistribution studies
  - Use of platform related stability data to support development
    - Is this necessary?

- Product development and characterization in parallel with early phase clinical studies
  - Case by case

- Enhanced engagement with stakeholders, e.g., vaccine manufacturers, clinical trial sponsors, national and international partners
  - At some level, yes
  - Critical human resource issue

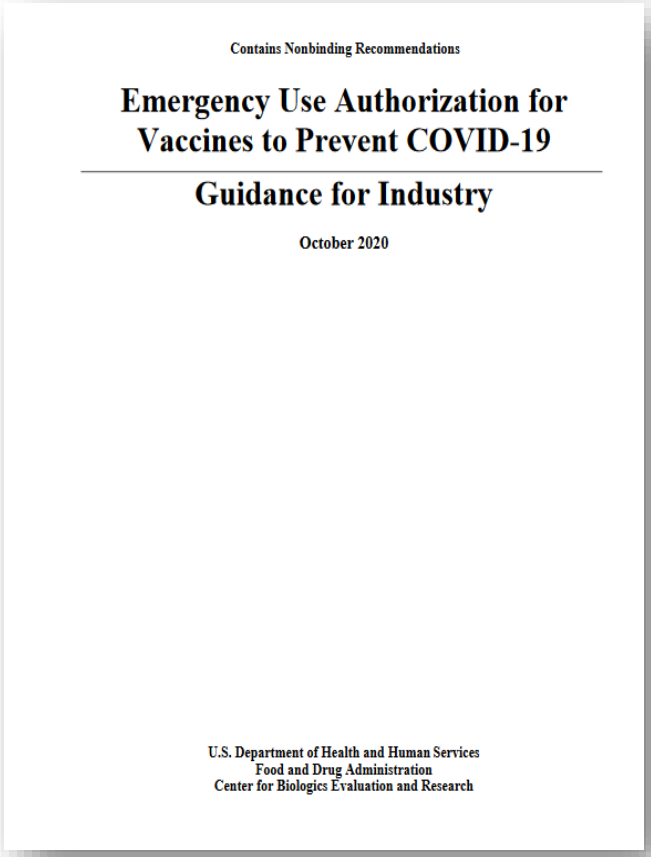
FDA Guidance for Industry: Development & Licensure of Vaccines to Prevent COVID-19 (June 2020)



- Helps facilitate the timely development of safe and effective vaccines to prevent COVID-19
- Reflects advice the FDA has been providing over the past several months to companies, researchers and others
- Describes the agency's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19

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

FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (February 2021)



Contains Nonbinding Recommendations

Emergency Use Authorization for Vaccines to Prevent COVID-19

Guidance for Industry

October 2020

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

- Reflects advice the FDA has been providing to vaccine developers
- Describes the Agency's current recommendations regarding the data needed to support issuance of an EUA for vaccines to prevent COVID-19
- Describes the Agency's current recommendations regarding the evaluation of vaccines to prevent COVID-19 caused by variants of concern

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

Thank You