COVID Vaccines: Expediting Development While Ensuring Product Quality

April 24, 2021
CMC Strategy Forum
China 2021 Pilot Program

Robin Levis, Ph.D.

Deputy Director,
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

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 to prevent COVID-19

Vaccine Development against Emerging Infectious Diseases

- Follows same paradigm as other preventive vaccines
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Establish product-related data and testing plans adequate to support the manufacturing process:
    - Characterize product quality attributes, including stability
    - Demonstrate consistency of manufacturing in a well qualified facility
    - Ensure quality systems are in place to ensure product quality
  - Pre-clinical data: supportive of initiating clinical studies
  - Human clinical data adequate to support the proposed indication and use
  - Post-licensure pharmacovigilance plan
- Unique considerations if development occurs in a public health emergency

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

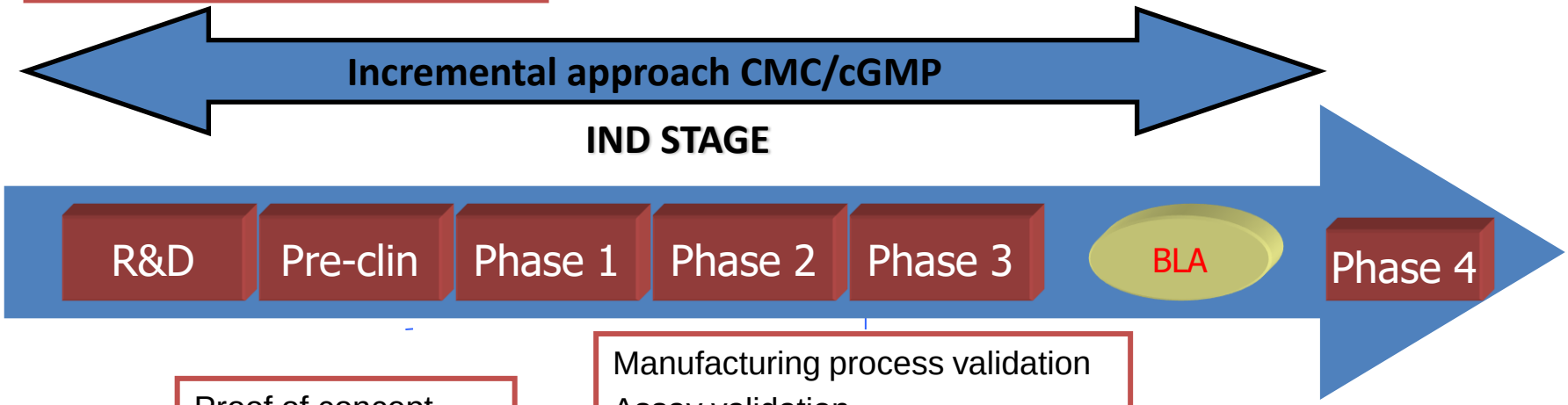
Unapproved product, or unapproved use of an approved product, in response to a public health emergency

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



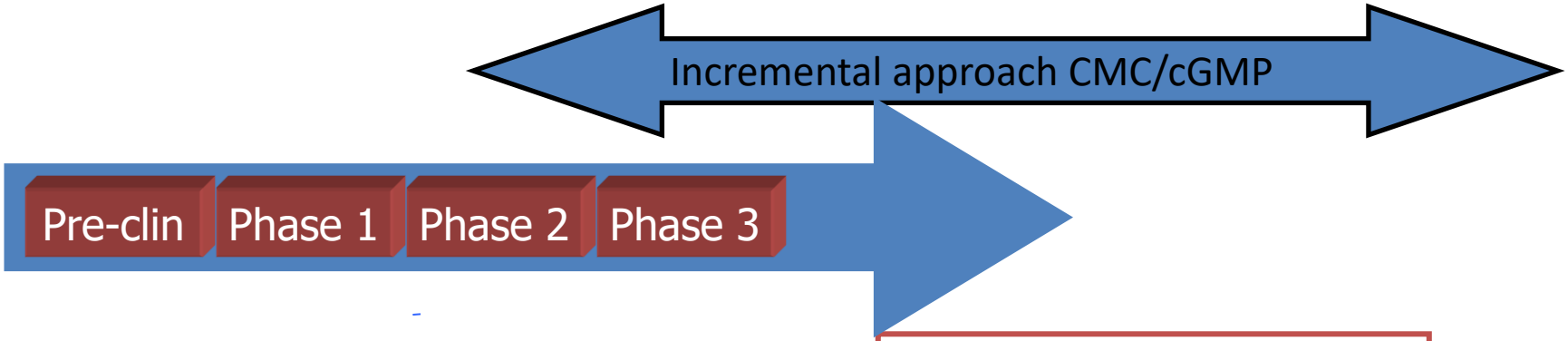
Proof of concept
Pre-clinical safety

Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

Vaccine Development: Expedited Development Pathway

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

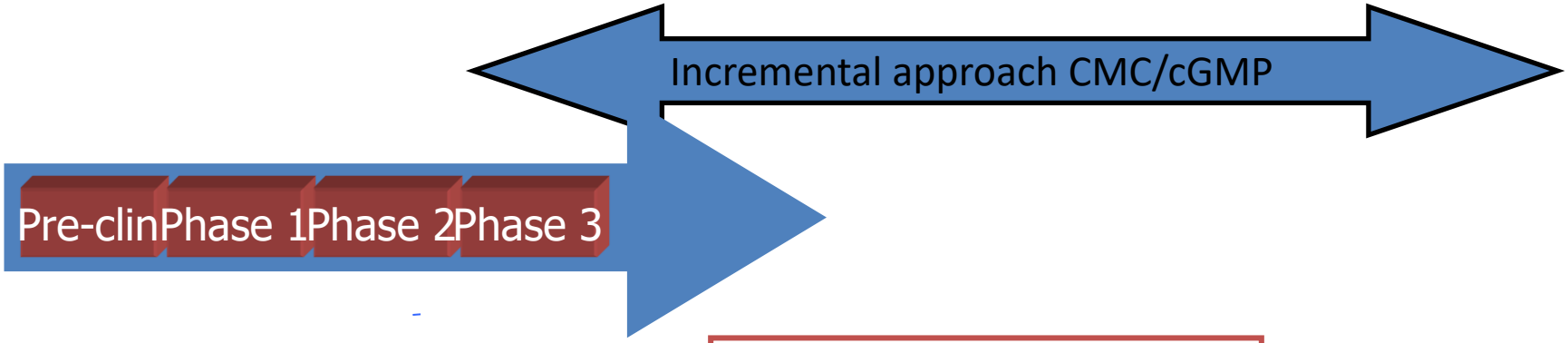


Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

Vaccine Development: Super Expedited Development Pathway

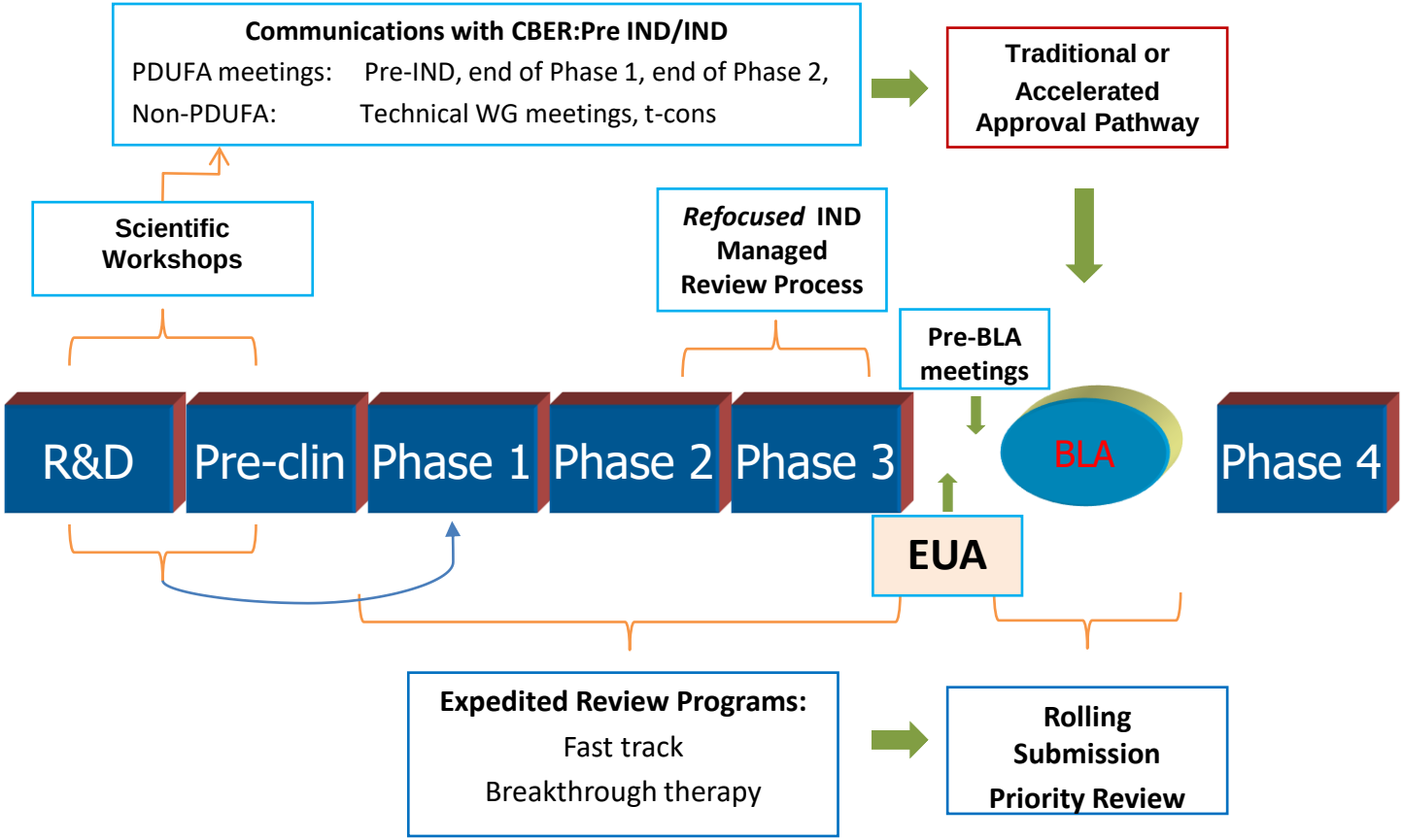
Process Development
- Source characterization
- Raw material qualification
- Cell bank characterization
- DS/DP characterization
- Assay development
- Formulation development
- Process controls

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

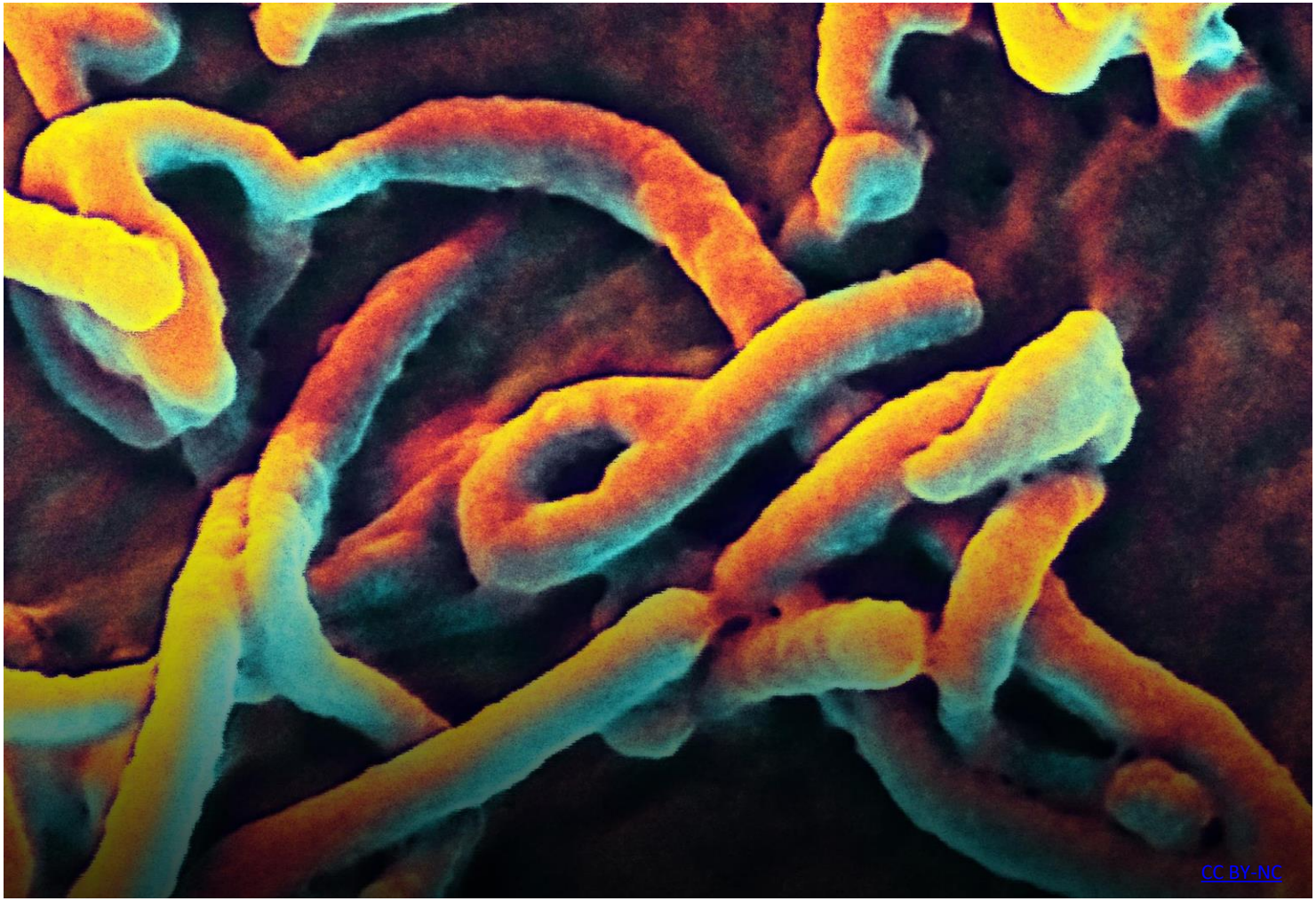


Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

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

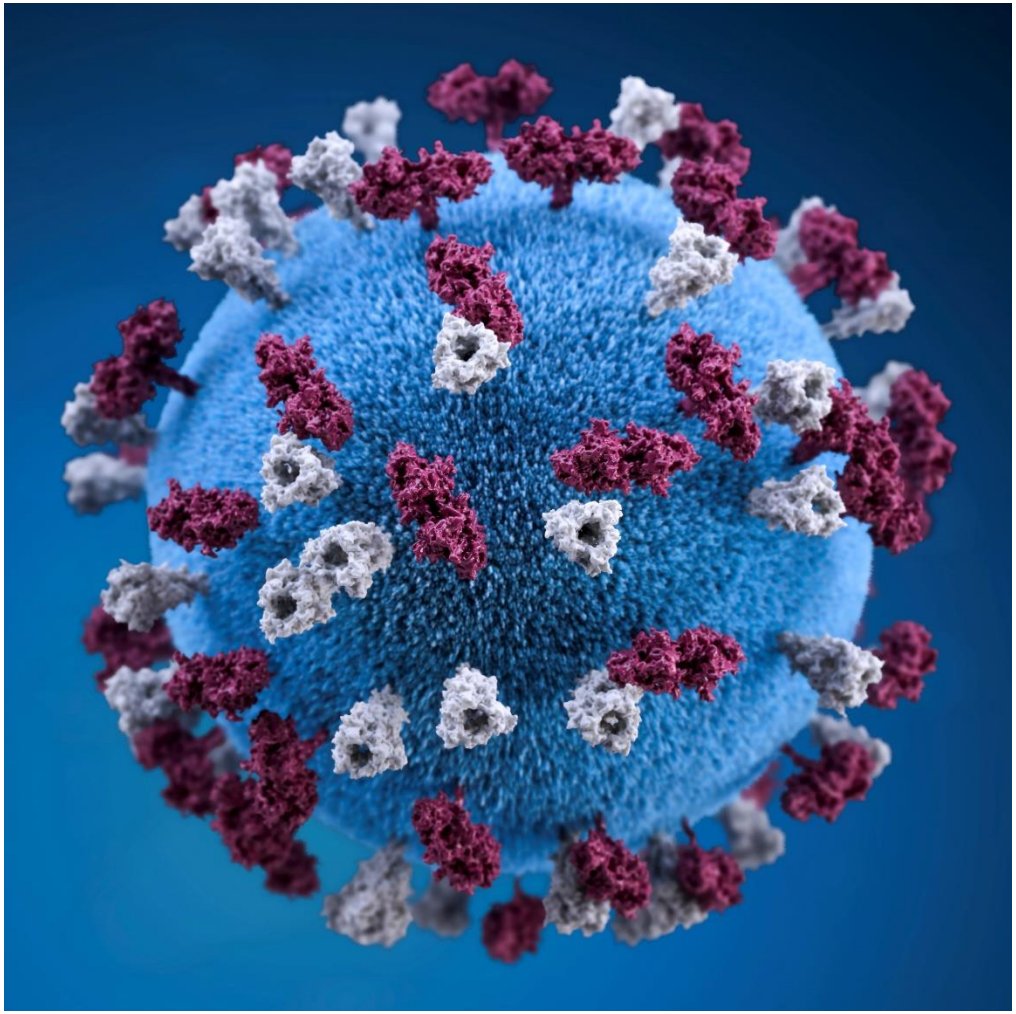
Regulatory and Scientific Issues in Ebola Vaccine Development - CMC

- Product characterization and pre-clinical 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
- 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 IND 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
- Post-marketing studies

COVID-19 Vaccine Development



Unique and Critical Considerations for COVID-19 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
  - Emergence of variant virus strains
- Establish minimum CMC, safety, clinical endpoints
- Use of EUA for vaccine access

COVID-19 Vaccine Development

- Development, authorization and licensure of vaccines against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks
- Numerous COVID-19 candidate vaccines (+250 globally) based on different platforms and technologies
  - E.g., RNA, DNA, protein subunit, inactivated virus, non-replicating and replicating viral vector, live attenuated, VLP
  - Express the spike protein or parts of the spike protein, i.e., the receptor binding domain (RBD), as the immunogenic determinant
- Many vaccine candidates, + 80, have entered Phase 1 and 2 clinical trials around the globe.
  - Many have advanced to Phase 3 clinical trials to evaluate their efficacy and safety
  - Some have been approved/authorized for use
- Critical to have global discussion and harmonization to facilitate rapid development, approval/authorization, and distribution

Considerations for COVID-19 Vaccines

- COVID-19 vaccines will be widely deployed and administered to billions of individuals - 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) and clinical data, including both safety and effectiveness data to support potential widespread use of these vaccines
- **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

- 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

- **FDA must ensure that vaccines that are approved or authorized under EUA are supported by adequate scientific and clinical data**

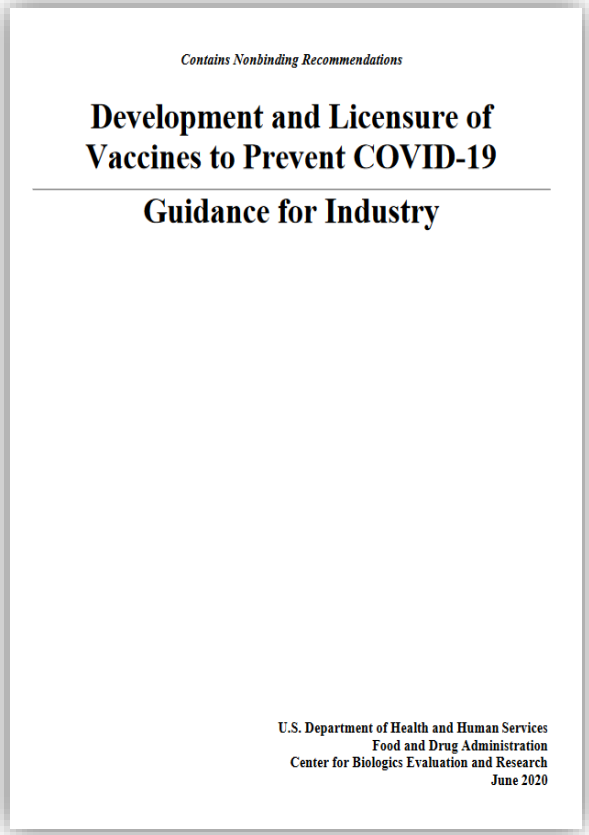
COVID-19 Vaccines: Development Strategy & Data Required to Support Licensure

- Nonclinical data
  - Nonclinical safety studies
    - Can rely on data from similar products using the same vaccine platform
  - Characterization of the immune response
    - Considered necessary for new antigen prior to Phase 1
  - Address the potential for vaccine-induced enhanced respiratory disease
    - Considered necessary for new antigen prior to Phase 1
- Adequate clinical data to support the proposed indication and use
  - Efficacy and safety
  - Characterization of the immune response
- Post-licensure pharmacovigilance plan

COVID-19 Vaccines: Development Strategy & Data Required to Support Licensure (cont.)

- Well defined manufacturing process to ensure product quality and consistency
- Product-related data and testing plans adequate to support the manufacturing process in an appropriate facility, characterize stability and ensure consistency of manufacture
- CMC and facility data:
  - Compliance with cGMP requirements
    - **Site visit**
  - Establishment of quality systems to support manufacturing
  - **Comparability data to support manufacturing in multiple facilities**
  - **Stability data to support initial use**

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

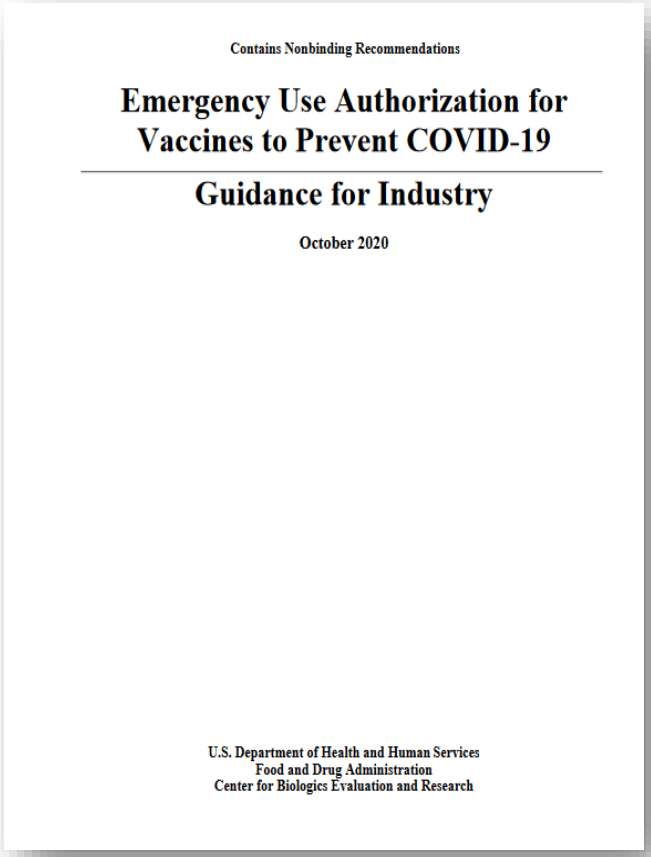
Emergency Use Authorization

- An Emergency Use Authorization (EUA) may be issued only after several statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-2))
- Issuance of an EUA requires a determination that the known and potential benefits of the **investigational** product outweigh its known and potential risks
- Use of an **investigational** COVID-19 vaccine under an EUA is not subject to informed consent requirements but vaccine recipients need to be provided a fact sheet that describes:
  - The investigational nature of the product
  - The known and potential benefits and risks
  - Available alternatives
  - Option to refuse vaccination

Emergency Use Authorization (cont.)

- An EUA for a COVID-19 vaccine may allow for rapid and widespread deployment for administration of the investigational vaccine to millions of individuals, including healthy people
- Issuance of an EUA for an investigational COVID-19 vaccine would require
  - Adequate manufacturing information to ensure the product's quality and consistency
    - CMC and Facility information
  - A determination that the benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial demonstrating safety and efficacy
- Any assessment regarding an EUA would be made on a case-by-case basis considering the proposed target population, the product characteristics, preclinical and human clinical data, and the totality of the available scientific evidence relevant to the product
- All products considered for use under an EUA will be presented to the public Advisory Committee for review and comment.

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

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*
- Determination of when a variant should be included in vaccine
- 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
- Regulatory pathway to approve or authorize use of new vaccines
- More to come…

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 approved for use under EUA).
- Vaccines against emerging infectious diseases will be licensed based on supportive clinical data.
  - 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.
  - This data will be critical for vaccines developed against SARS-CoV-2 variants.
- Global response is critical
- 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.

Thank You