Regulatory Challenges: Expediting CMC Development While Ensuring Product Quality

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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 to prevent COVID-19

Vaccine Development against Emerging Infectious Diseases

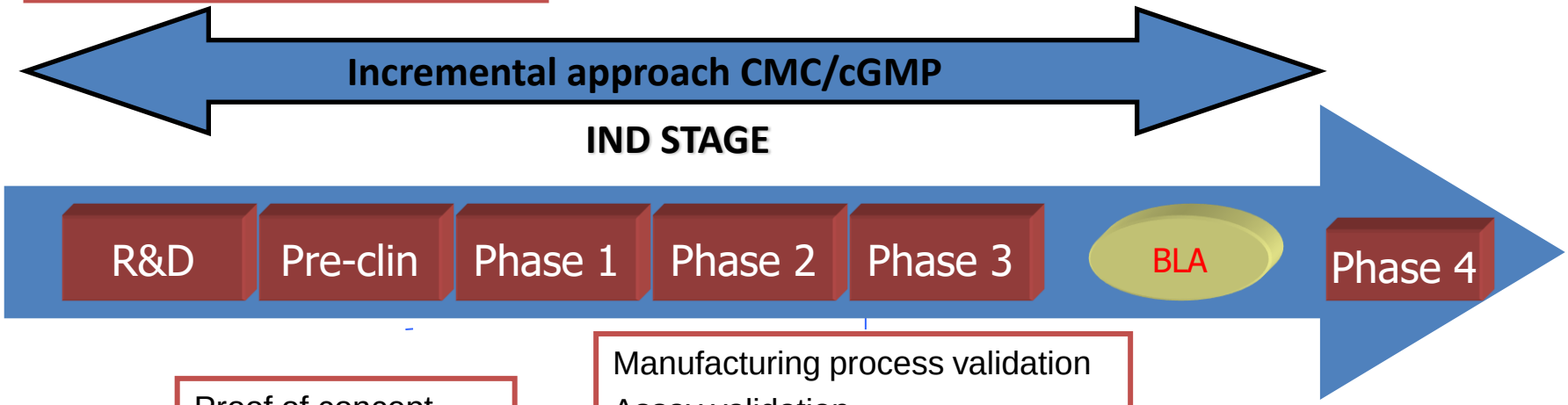
- Follows same paradigm as other preventive vaccines
  - Unique considerations if development occurs in a public health emergency
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Product-related data and testing plans adequate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

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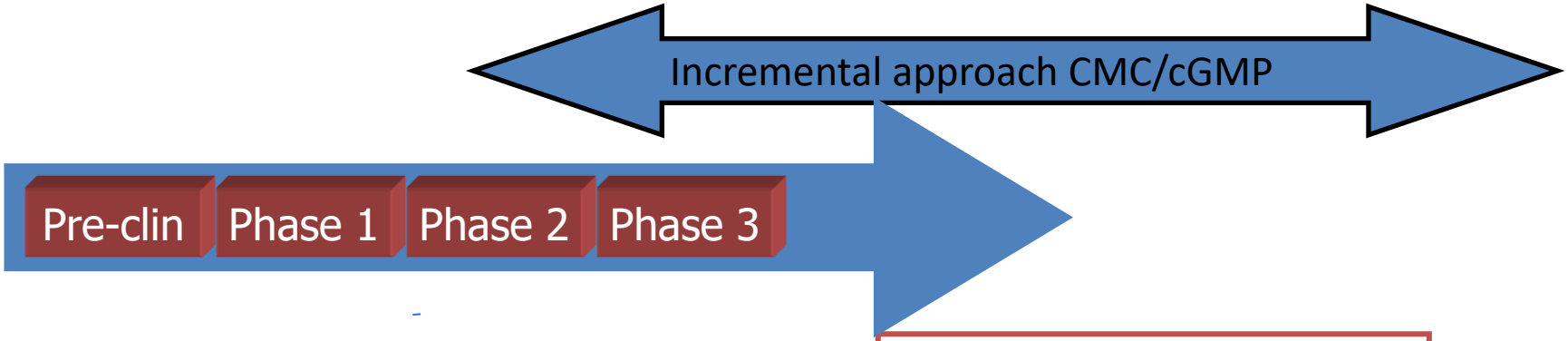

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Vaccine Development: Super Expedited Development Pathway

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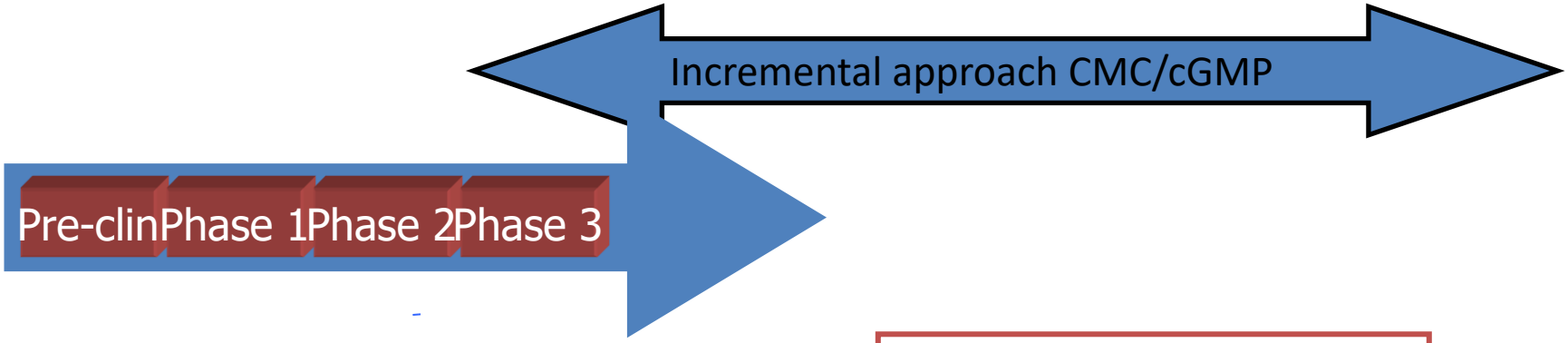

Manufacturing process validation
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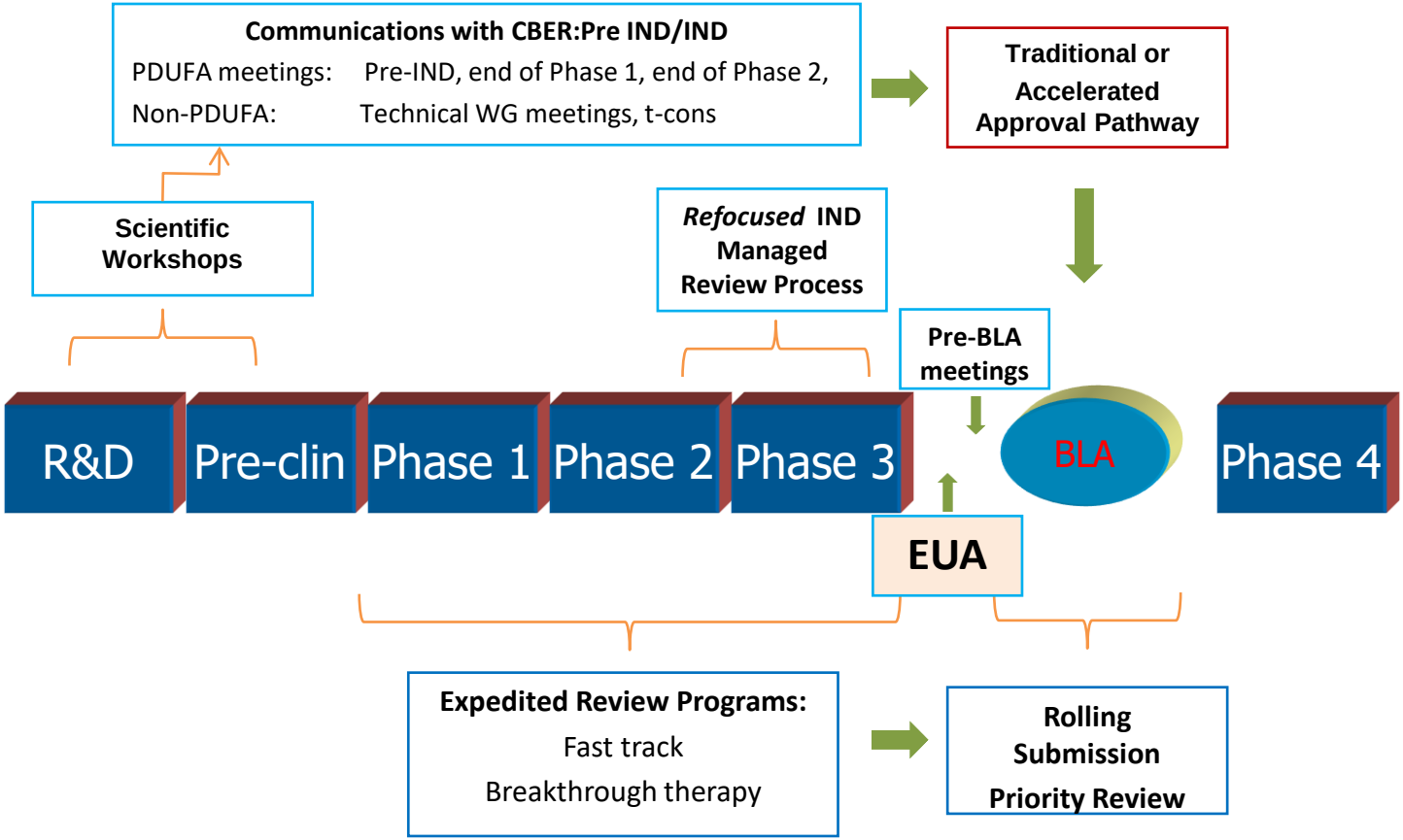
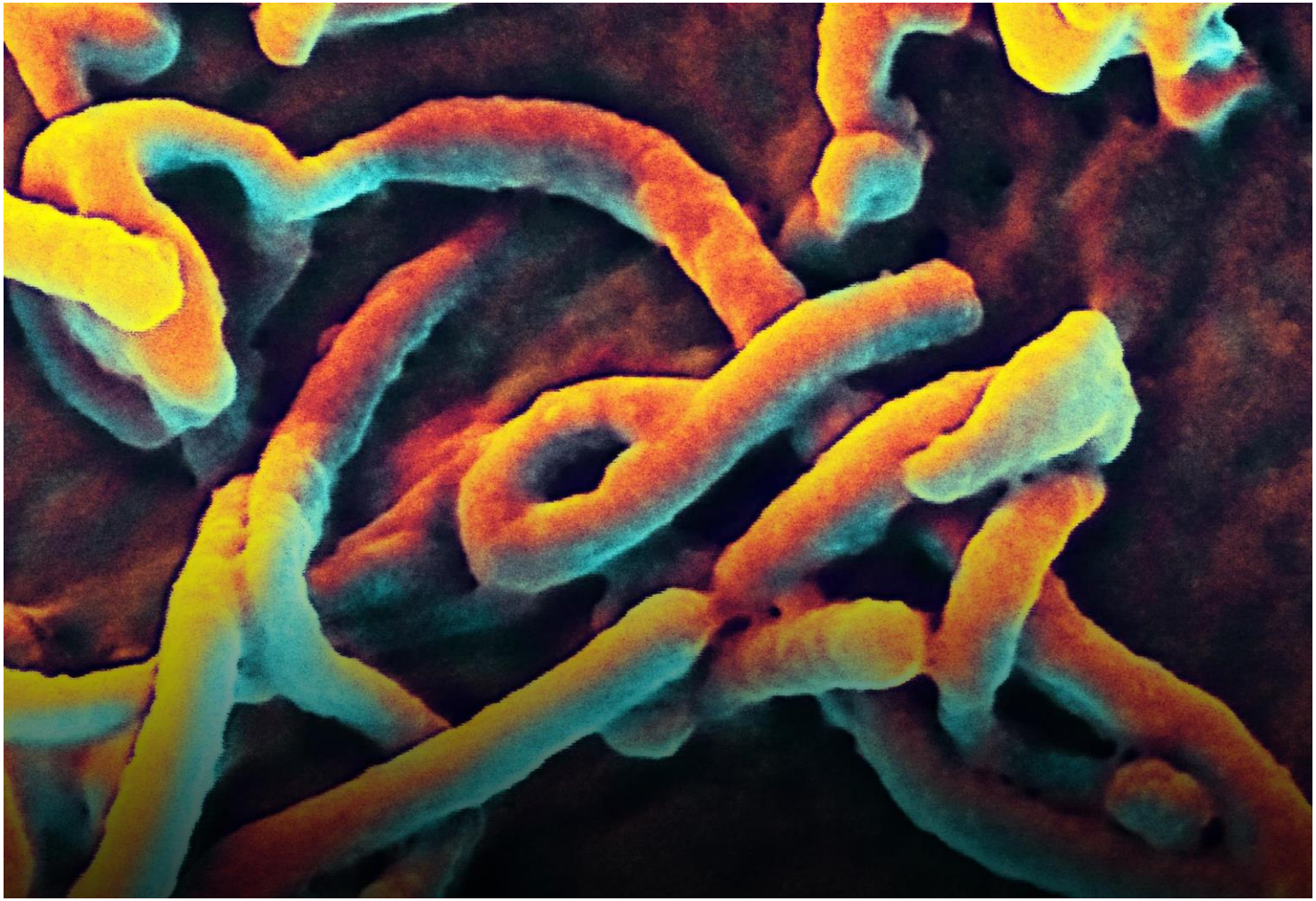
Strategies for Accelerating Vaccine Approval



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 and licensure pathways might differ

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 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

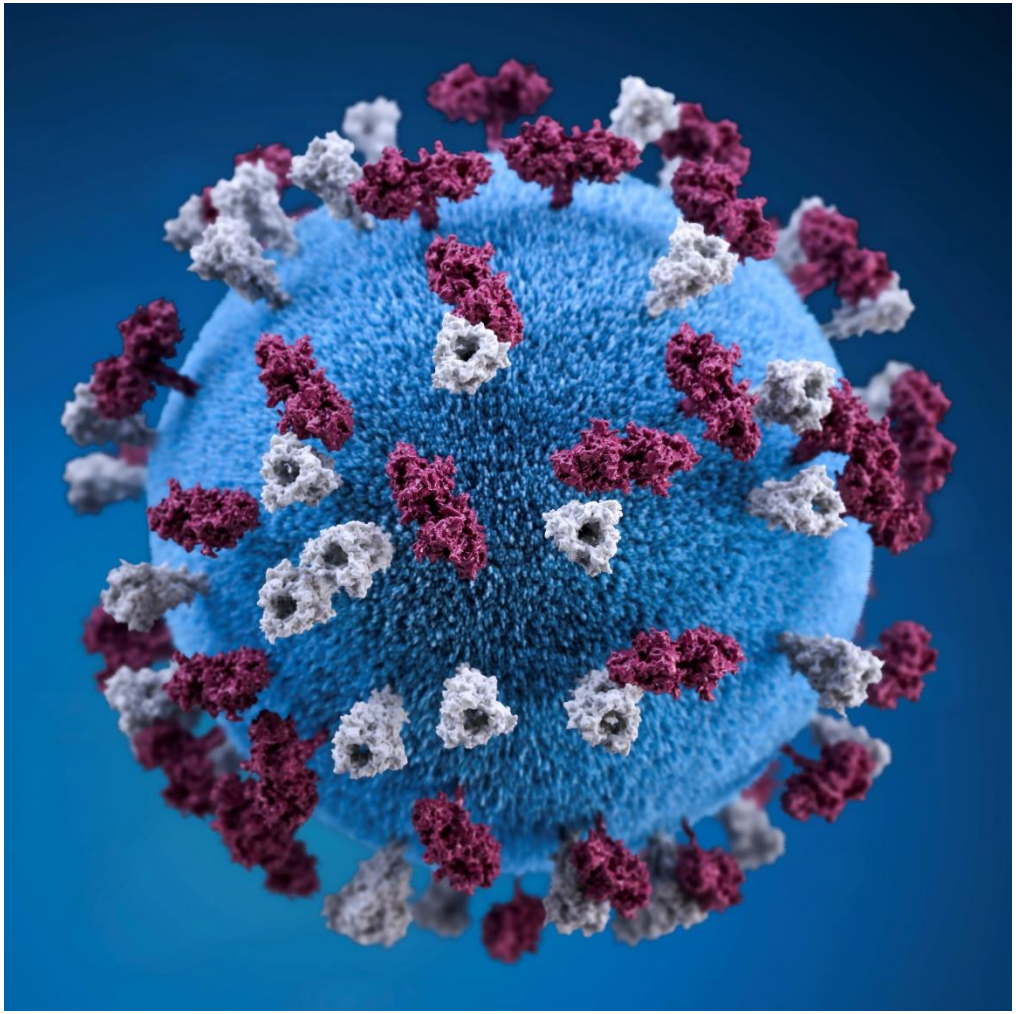
Regulatory and Scientific Issues in Ebola Vaccine Development - CMC

- 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

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 while maintaining confidentiality
  - 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



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
- 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-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 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 have entered Phase 1 and 2 clinical trials around the globe and some have advanced to Phase 3 clinical trials to evaluate their efficacy and safety

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 must ensure that vaccines that are approved or authorized under EUA are supported by adequate scientific and clinical data**
- FDA is facilitating COVID-19 vaccine development by
  - Providing expedited reviews of CMC 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

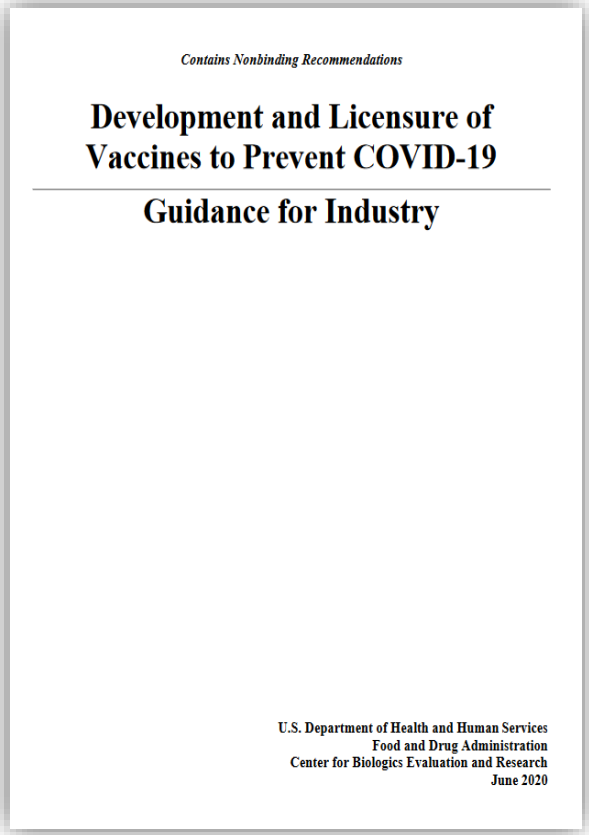
Considerations for COVID-19 Vaccines

- COVID-19 vaccines will be widely deployed and administered to millions of individuals, including healthy people
- Public expectation that COVID-19 vaccines will be safe and effective
  - Low tolerance for vaccine-associated risks
- **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**
- Vaccine development can be expedited; however, there needs to be sufficient time to accrue adequate manufacturing, safety and effectiveness data to support potential widespread use of these vaccines

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

- 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
- Nonclinical data
  - Nonclinical safety studies
  - Characterization of the immune response
  - Address the potential for vaccine-induced enhanced respiratory disease
- Adequate clinical data to support the proposed indication and use
  - Efficacy and safety
  - Characterization of the immune response
- CMC and facility data: compliance with cGMPs requirements
- Post-licensure pharmacovigilance plan

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

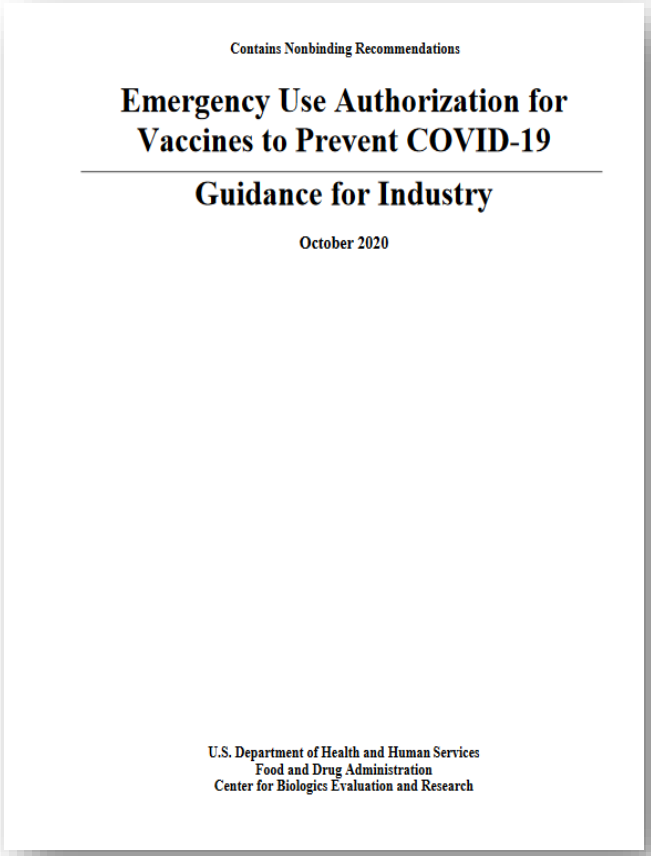
Emergency Use Authorization

- 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
  - 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

FDA Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020)


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

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 approved for use under EUA).
- Vaccines against emerging infectious diseases will 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. FDA is committed to make safe, efficacious vaccines available during public health emergencies.
- 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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Thank You