Regulating Vaccines During COVID-19

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FDA U.S. FOOD & DRUG ADMINISTRATION

Overview

Vaccine Development

- Pathways to expedite review and licensure
- FDA/CBER's role in facilitating vaccine development

Key considerations for vaccines during COVID-19 pandemic

- Emergency Use Authorized (EUA) & Approved COVID-19 CBER regulated products

Regulatory opportunities and challenges in vaccine development

Lessons learned to support the accelerated development of *vaccines for future application*

Vaccine Development against Emerging Infectious Diseases

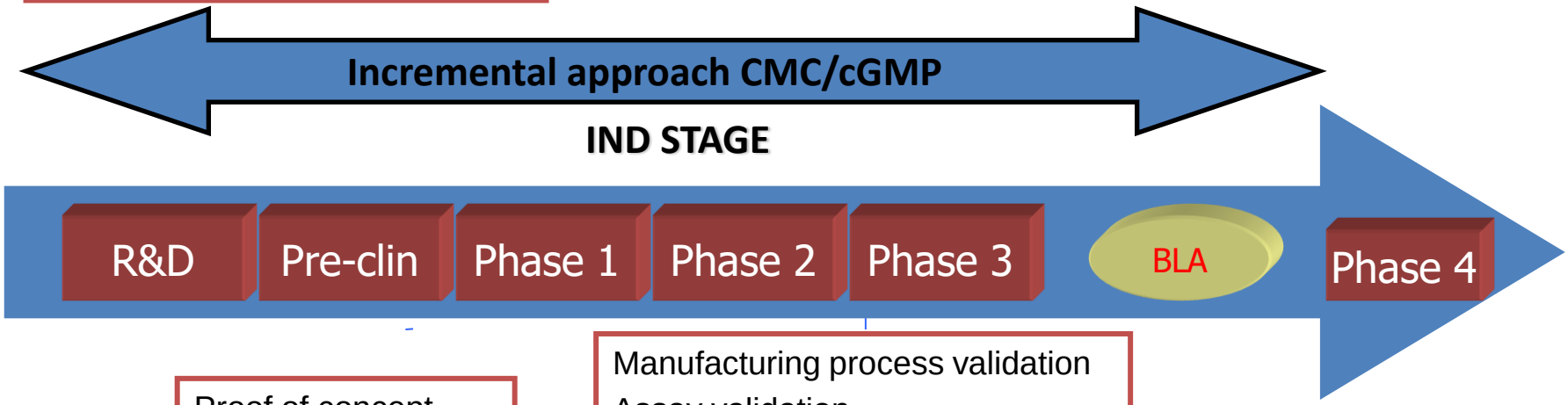
- Follows same paradigm as other preventive vaccines
  - Unique considerations if development occurs in a public health emergency
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Product-related data and testing plans adequate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

Process Development
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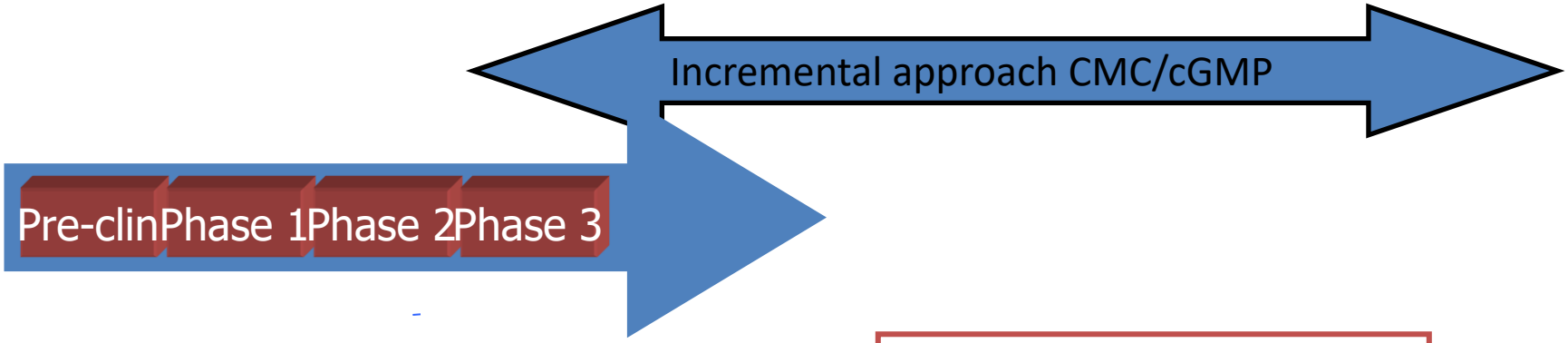

Manufacturing process validation
Assay validation
Final product specification
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Facilitating Expedited Vaccine Development - Role of FDA/CBER

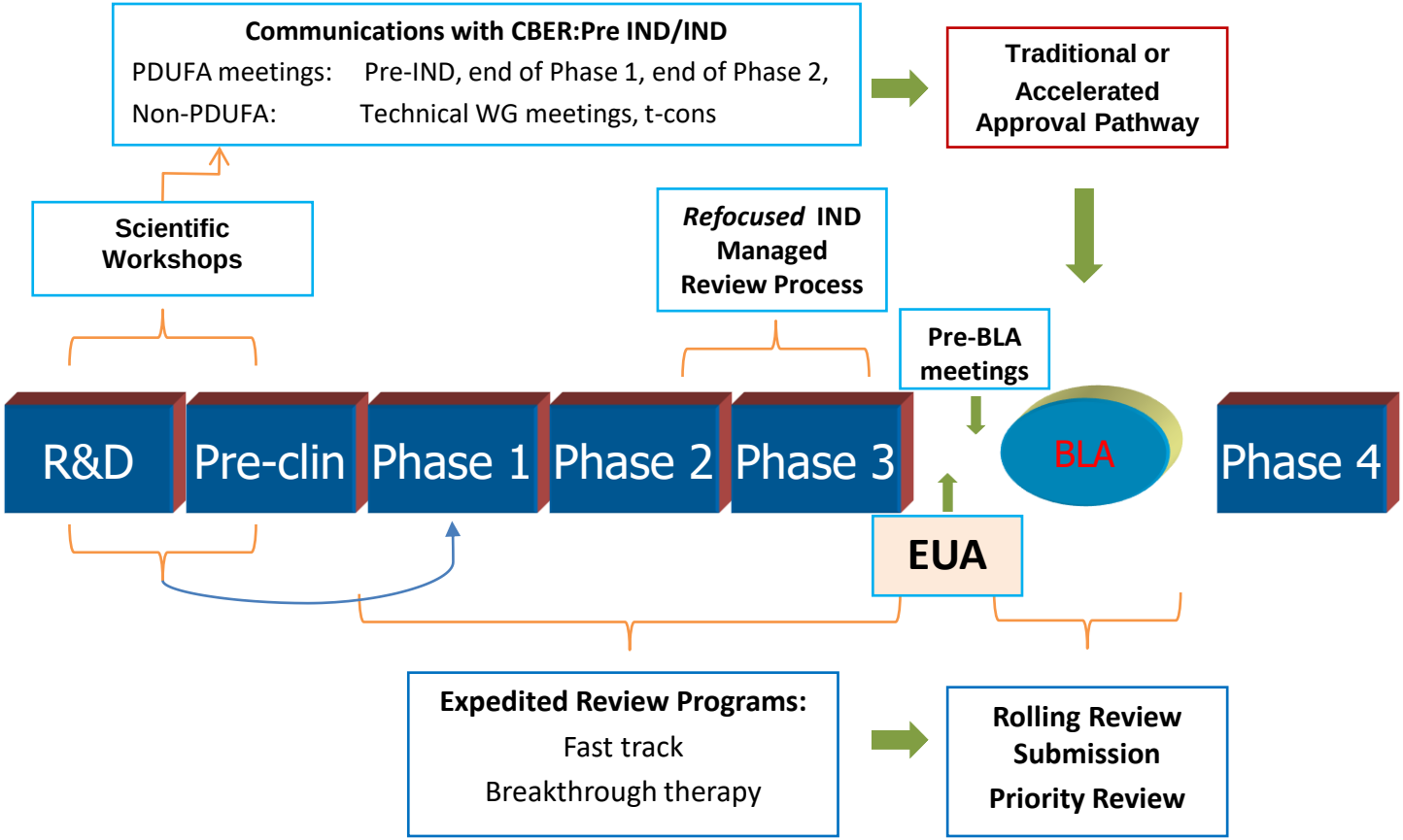
When confronted with an emerging disease with significant public health impact, FDA provides:

- Expedited review of chemistry, manufacturing and controls (CMC) information, preclinical and clinical protocols, and clinical trials data, where available

- Numerous meetings and pathways to licensure for vaccines: Accelerated Approval, Fast Track, Rolling Review Submission, Breakthrough Therapy and Priority Review

- Special emergency programs
  - Emergency Use Authorization for products used in US population
  - Coronavirus Treatment Acceleration Program (CTAP) *for therapeutics*
    - https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap

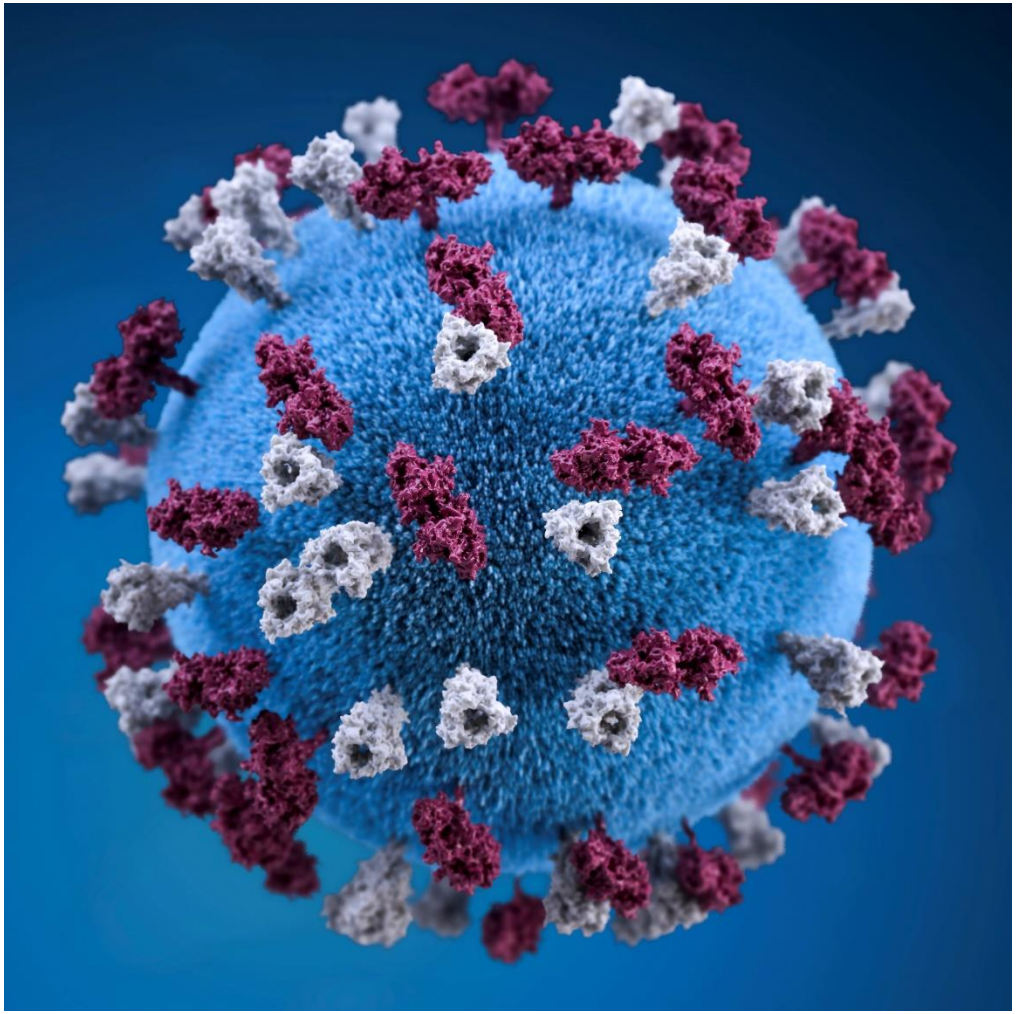
Strategies for Accelerating Vaccine Approval



Facilitating Expedited Vaccine Development - Role of FDA/CBER (cont.)

- International collaboration among regulatory agencies in review, with goal of regulatory convergence
- Engage in scientific collaboration with industry and academia
  - CBER Participation in the evaluation of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody:
  - https://cdn.who.int/media/docs/default-source/biologicals/ecbs/bs-2020-2403-sars-cov-2-ab-ik-17-nov-2020_4ef4fdae-e1ce-4ba7-b21a-d725c68b152b.pdf?sfvrsn=662b46ae_8&download=true
- FDA Vaccines Advisory Committee public meetings when necessary
  - Expert advice
  - Transparency for public awareness of critical issues

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

Authorized & Approved COVID-19 CBER Regulated Products
(As of November 22, 2021)

Office of Vaccines Research and Review (OVRR)

- Pfizer-BioNTech mRNA COVID-19 Vaccine, Comirnaty (2 dose series, plus 1 booster)
  - EUA issued December 11, 2020 for individuals ≤ 16 years
  - EUA Authorized for children and adolescents ages 5-15 years
  - EUA Authorized additional primary dose for certain immunocompromised individuals
  - **Licensed August 23, 2021**

- Moderna mRNA COVID-19 Vaccine (2 dose series, plus 1 booster)
  - EUA issued December 18, 2020 for individuals ≥ 18 years
  - EUA Authorized additional primary dose for certain immunocompromised individuals

- Janssen COVID-19 Vaccine (1 dose series, plus 1 booster)
  - EUA issued February 27, 2021
  - EUA Authorized for single booster of any authorized vaccine after completion of primary dose to ≥ 18 years

November 19, 2021 - All 3 vaccines are EUA Authorized for heterologous use ("mix and match") booster dose in eligible populations 18 years and older with currently available FDA-authorized/approved COVID-19 vaccines (Pfizer-BioNTech, Moderna, Janssen)

Authorized & Approved COVID-19 CBER Regulated Products (As of November 22, 2021)

Office of Blood Research and Review (OBRR)

- Convalescent Plasma
  - EUA issued April 23, 2020, for treatment of hospitalized patients with COVID-19

Office of Tissues and Advanced Therapies (OTAT)

- No EUA or licensed COVID-19 products

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 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

Regulatory and Scientific Issues in Emerging Virus Vaccine Development - CMC

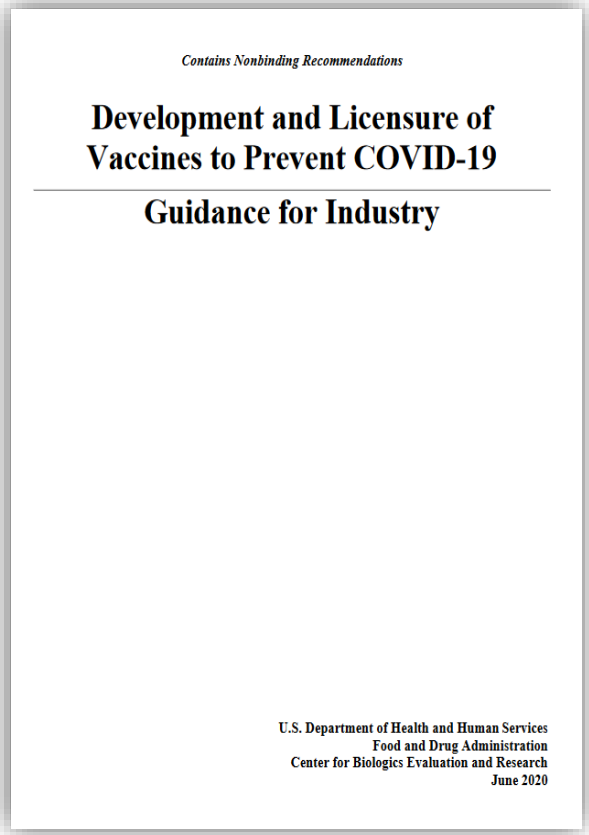
- Product characterization and testing
  - Supportive data from platform-related products
  - Exceptions to testing of extraneous agents (viral pathogens, mycoplasmas)
    - Suitability and safety of product otherwise established (adventitious agent testing)
- Initial specifications for some assays based 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

Licensure of a Product used Under Emergency Use Authorization

- Finalize validation data
  - Process validation
  - Assay and analytical test validation
- Demonstrate manufacturing consistency and comparability between manufacturing sites
- Clinical safety data for longer period of time

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

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

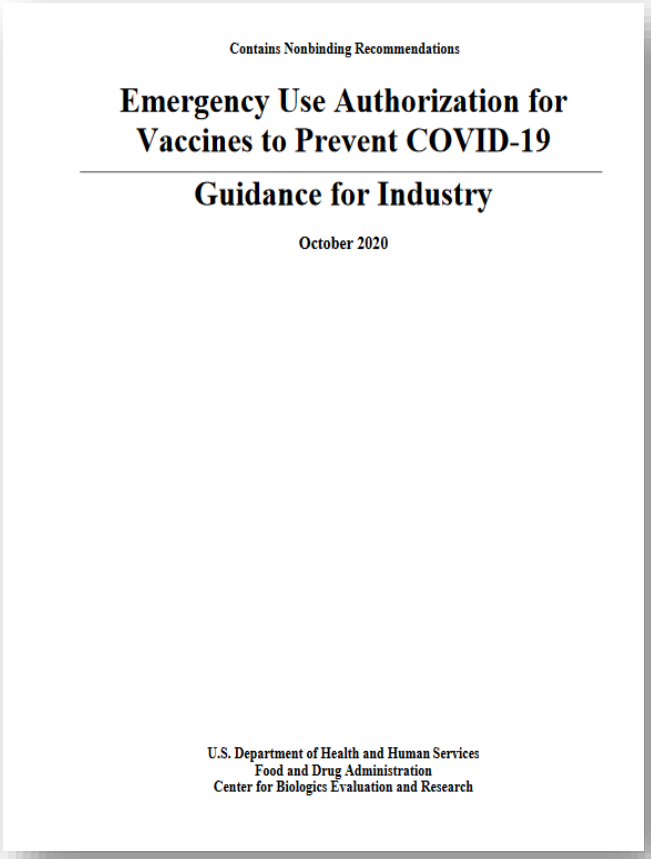


- Helps facilitate the timely development of safe and effective vaccines to prevent COVID-19
- Reflects advice the FDA has been providing over the past several months to companies, researchers and others
- Describes the agency's current recommendations regarding the data needed to facilitate clinical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

COVID-19 Vaccine Guidances: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

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

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



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

COVID-19 Vaccine Guidances: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

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

Regulatory Opportunities and Challenges

Opportunities

- CBER's science-based regulators had pre-existing expertise with nucleic acid - based vaccines
- Attention to health inequalities
- Resources to develop and expand vaccine production globally using CMOs
- Rewarding "essential" work

Challenges

- Limited staff, multiple submissions at the same time, urgency for review completions
- Workload distribution: review of non-prioritized and non-COVID products
- Assuring manufacturing comparability across sites with limited physical access to inspect manufacturing sites
- High expectations and pressure from all sides

Key Considerations for Expedited Vaccines

- Vaccine approval will be based on validated and well-controlled manufacturing process
- Vaccine approval will be based on adequate and well-controlled studies demonstrating safety and effectiveness
- Future expedited vaccines 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 will be data-driven**

"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
    - 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
  - Critical for global response
  - Harmonized response from regulators
    - At some level, yes
    - Critical human resource issue

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

Thank You!