# Regulatory Considerations for Keeping Things Moving

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# 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) & Licensed COVID-19 CBER regulated products under a Biologics License Application (BLA)

**Summary of development timelines for two COVID vaccines**

**Key considerations for going from EUA to full licensure**

**How do we apply lessons learned**

# US Regulatory Framework to Make Vaccines Available During Public Health Emergency

**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 against Emerging Infectious Diseases

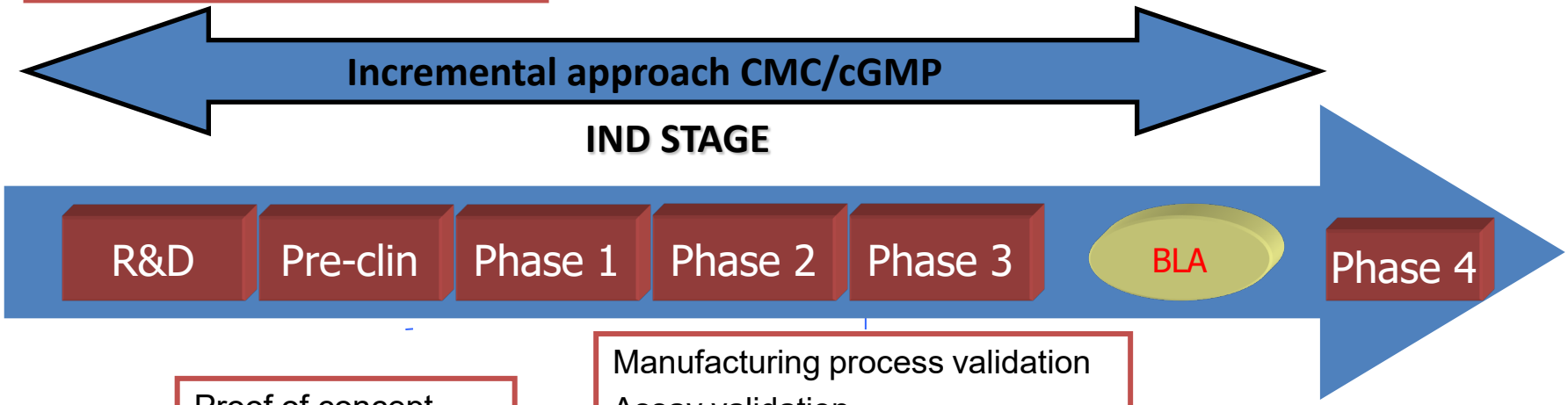
- Follows same paradigm as other preventive vaccines
  - Unique considerations if development occurs in a public health emergency
- Development Strategy
  - Develop and refine manufacturing process to ensure quality product and consistency of manufacture
  - Product-related data and testing plans adequate 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 safety and 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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**Process Optimization**
- In-process controls
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***Incremental approach*** CMC/cGMP

Pre-clin Phase 1 Phase 2 Phase 3

Manufacturing process validation
Assay validation
Final product specification
Final formulation
Stability

# 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

- Early, expedited review of manufacturing and testing facilities

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

- International collaboration among regulatory agencies in review, with goal of regulatory convergence

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

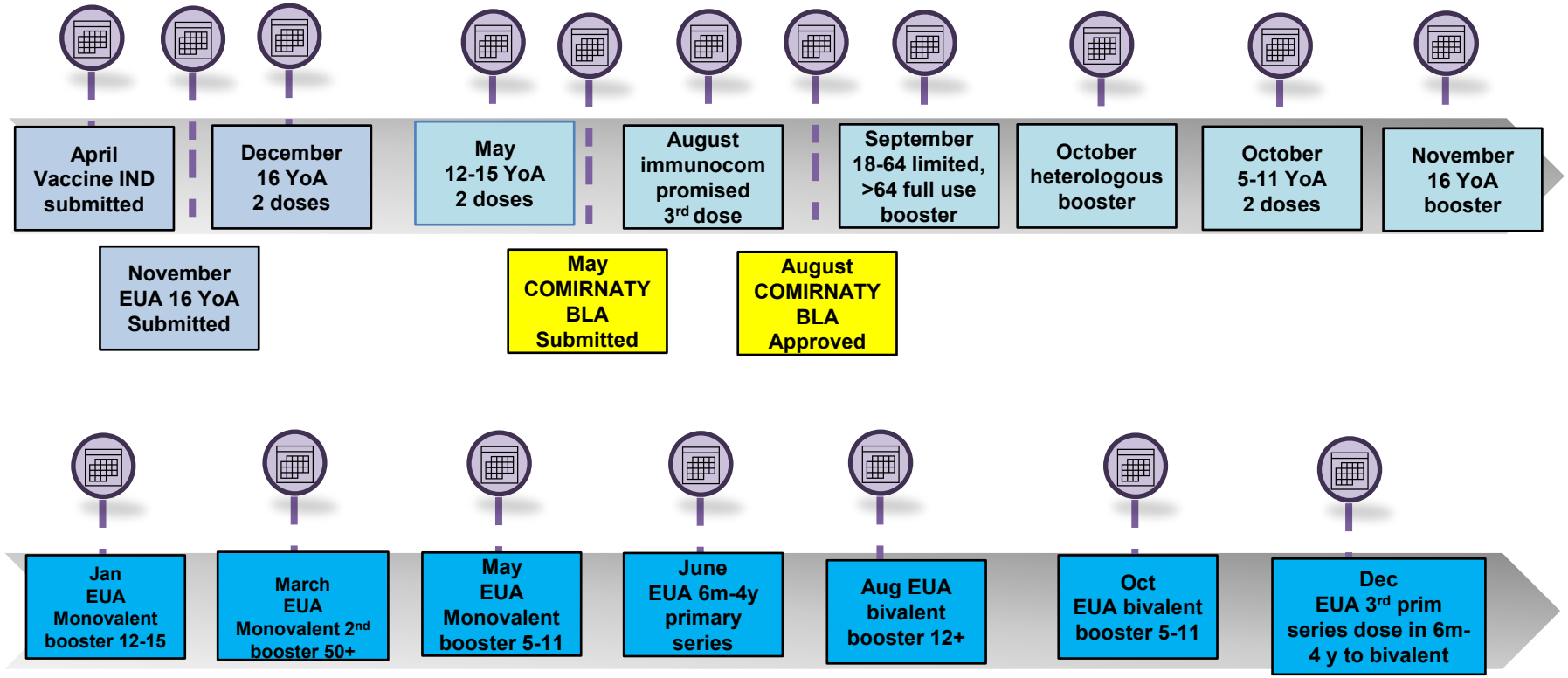
- Engage in scientific collaboration with industry and academia
  - CBER Participation in the evaluation of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody
- FDA Vaccines Advisory Committee public meetings when necessary
  - Expert advice
  - Transparency for public awareness of critical issues
- **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

# 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**

# Pfizer-BioNTech COVID-19 Vaccine

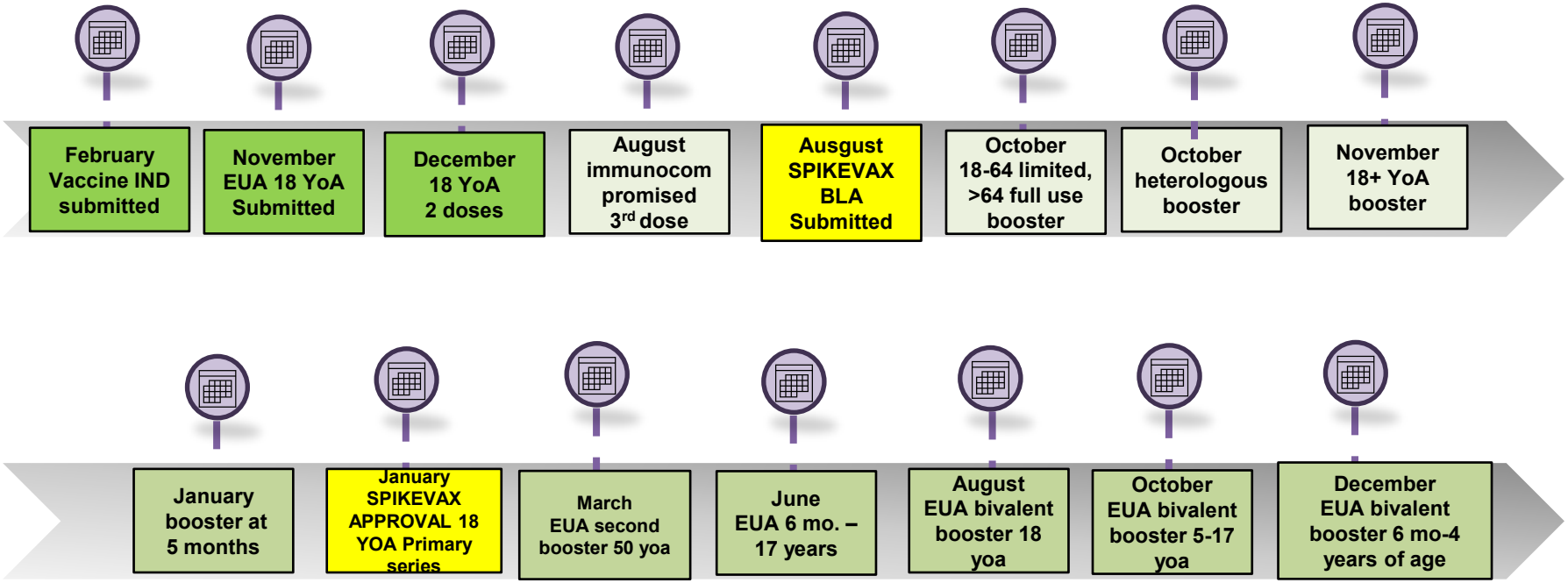
## Development Timeline 2020 - 2022




Comirnaty and Pfizer-BioNTech COVID-19 Vaccine | FDA

# Moderna COVID-19 Vaccine

## Development Timelines 2020 - 2022




[Spikevax and Moderna COVID-19 Vaccine | FDA]

# Transition to licensure - BLA

# Considerations for EUA to BLA

- CMC Data – Complete process development and validation, establishment of shelf life
- Product quality and testing – Establish Lot Release Protocol
- Manufacturing Facilities – Is there cGMP compliance?
- Products used under both EUA and BLA – Why is this necessary? How long will the EUA be needed?
- Clinical Data – Are the study reports finalized? Is there sufficient safety and effectiveness data to support licensure?

# EUA to BLA – CMC data

- Finalize process validation
  - Process validation completed for both drug substance and drug product
  - Full final study reports for assay and analytical test validation
- Establishment of shelf life
  - Data to support expiry dating of drug product
- Demonstrate manufacturing consistency and comparability between manufacturing sites

# EUA to BLA – Lot Release

- No official lot release occurs under EUA
  - Final lot CoAs are reviewed prior to product distribution under EUA.
- Finalize lot release protocol and required testing to be performed by the sponsor and by CBER
  - Establish administrative structure for the submission of lot release protocols and samples. Most important for new sponsors.
  - Critical to determine the suitability of analytical methods used for release of DS and DP. Review final validation reports.
  - Establish and implement release test methods in CBER quality control laboratory.
  - Perform testing and data review of “launch” lots and all subsequent lots to be distributed.

# EUA to BLA - Facilities

- Quality of facility to manufacture product for use under EUA
  - Review performed according to requirements for products under development – IND
  - For EUA review, there is an expectation the cGMPs are in place.
    - These expectations are detailed in the EUA Guidance
  - Depending on the situation, can perform:
    - Site visit – no 483 issued, no classification in the compliance system
    - Investigation
    - Inspection
  - Decision made on a case by case basis and depends on:
    - Inspectional history

- Requirements for licensure of a facility under BLA
  - Expectation that all quality systems are in place

# What's next?

# "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
- **Can we apply these activities to future, new products under development?**

# Applying "Lessons Learned"

- **FDA must ensure that vaccines that are approved or authorized under EUA are supported by adequate scientific and clinical data**
- Vaccine development may be facilitated based on knowledge gained from similar products and platform technologies
- Use of analytical data to support product comparability, quality and stability across manufacturing sites
- Use of analytical data to support lot-to-lot consistency
- FDA can facilitate vaccine development by
  - 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 vaccines through EUA
  - Directing efforts at generating adequate data to support full product licensure through BLA review

# Considerations going forward

- Is there a new “normal”?
- Are we ready for the next pandemic?
- Use of accelerated review pathways – how and when
- Resources needed to maintain current level of review engagement
- New technologies
- New ICH initiatives
  - Lots of ongoing activity across all documents
    - Implementation
    - Updates
- New legislative initiatives
  - How will these be incorporated into current review strategies
  - Will they be applicable to all product types, including vaccines