Regulatory Considerations for Moving from Emergency Use Authorization to Biological License Application for U.S. Products

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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)

Key considerations for going from EUA to full licensure

Summary of development timelines for two COVID vaccines

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

<table>
<thead>
<tr>
<th>Licensure</th>
<th>IND</th>
<th>EUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Approval</td>
<td><strong>Unapproved product</strong> with no, or limited, human safety and effectiveness data</td>
<td><strong>Unapproved product</strong>, or unapproved use of an approved product, in response to a public health emergency</td>
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<tr>
<td>Accelerated Approval</td>
<td>Expanded access use options</td>
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<td>Animal Rule</td>
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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

Incremental approach CMC/cGMP

IND STAGE

R&D | Pre-clin | Phase 1 | Phase 2 | Phase 3 | BLA | Phase 4

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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Incremental approach CMC/cGMP

Manufacturing process validation
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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
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
Considerations for EUA to BLA

• CMC Data – What is still needed?
• 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 (see below).
  - 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
# Pfizer-BioNTech COVID-19 Vaccine

## Development Timeline

<table>
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<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>Apr 22, 2020</td>
<td>Vaccine IND submitted</td>
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<tr>
<td>Dec 11, 2020</td>
<td>EUA 16 YoA 2 doses</td>
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<tr>
<td>Nov 20, 2020</td>
<td>COMIRNATY BLA Submitted</td>
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<tr>
<td>May 17, 2022</td>
<td>5-11 YOA booster</td>
</tr>
<tr>
<td>May 18, 2021</td>
<td>COMIRNATY BLA Submitted</td>
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<tr>
<td>Aug 12, 2021</td>
<td>Immunocompromised 3rd dose</td>
</tr>
<tr>
<td>Sep 22, 2021</td>
<td>OCT 18YOA 18-64 limited, &gt;64 full use booster</td>
</tr>
<tr>
<td>Oct 20, 2021</td>
<td>Heterologous booster</td>
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<tr>
<td>Oct 29, 2021</td>
<td>OCT 18YOA 5-11 YOA 2 doses</td>
</tr>
<tr>
<td>Nov 19, 2021</td>
<td>OCT 18YOA 16 YOA booster</td>
</tr>
<tr>
<td>Jan 3, 2022</td>
<td>OCT 18YOA 12-15 YOA booster</td>
</tr>
<tr>
<td>Jun 17, 2022</td>
<td>OCT 18YOA &gt;6 mo-4 YOA 2 doses</td>
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Comirnaty and Pfizer-BioNTech COVID-19 Vaccine | FDA


• 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

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 years 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

Key Considerations for Full Licensure of Expedited Vaccines - Summary

• The regulatory review of each vaccine will be data-driven
• 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
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Thank You!