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>Unapproved product, or unapproved use of an approved product, in response to a public health emergency</td>
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<td>Accelerated Approval</td>
<td>Expanded access use options</td>
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<tr>
<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

**Incremental approach CMC/cGMP**

**IND STAGE**

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<tr>
<th>R&amp;D</th>
<th>Pre-clin</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>BLA</th>
<th>Phase 4</th>
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- Proof of concept
- Pre-clinical safety

**Manufacturing process validation**
- Assay validation
- Final product specification
- Final formulation
- Stability

**BLA Supplement:**
- Manufacturing changes
- Formulation changes
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

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
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


• 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!