Regulating Vaccines During COVID-19

December 6, 2021

Cassandra Overking, MPH
Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and 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

**Incremental approach CMC/cGMP**

**IND STAGE**

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

**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**
- 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

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

Pre-clinPhase 1Phase 2Phase 3
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
Strategies for Accelerating Vaccine Approval

Communications with CBER: Pre IND/IND
- PDUFA meetings: Pre-IND, end of Phase 1, end of Phase 2,
- Non-PDUFA: Technical WG meetings, t-cons

Traditional or Accelerated Approval Pathway

Scientific Workshops

Refocused IND Managed Review Process

Pre-BLA meetings

BLA

R&D Pre-clin Phase 1 Phase 2 Phase 3 EUA

Expedited Review Programs:
- Fast track
- Breakthrough therapy

Rolling Review Submission Priority Review

Phase 4
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-b21ad725c68b152b.pdf?sfvrsn=662b46ae_8&download=true](https://cdn.who.int/media/docs/default-source/biologicals/ecbs/bs-2020-2403-sars-cov-2-ab-ik-17-nov-2020_4ef4fdae-e1ce-4ba7-b21ad725c68b152b.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

<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>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>Expanded access use options</td>
<td></td>
</tr>
<tr>
<td>Animal Rule</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)


- 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


- 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 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!