Expedited Product Development: Application of Regulatory Lessons Learned

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Overview

General considerations for vaccines
• Pathways to expedite review and licensure
• Pre-licensure development
• Approval pathways

Development of vaccines against emerging infectious diseases
• Early lessons learned from Ebola virus vaccine development during public health emergency
• Applicability of lessons learned to support the accelerated development of vaccines to prevent COVID-19
• What’s next?
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

- 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 - Ebola

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Pre-clin Phase 1 Phase 2 Phase 3

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Vaccine Development: Expedited Development Pathway - COVID

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Pre-clinPhase 1Phase 2Phase 3

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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

Refocused IND Managed Review Process

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

Pre-BLA meetings

BLA

EUA

Expedited Review Programs:
- Fast track
- Breakthrough therapy

Traditional or Accelerated Approval Pathway

Rolling Submission Priority Review
Ebola Virus Vaccine Development
Facilitating Ebola Vaccine Development - Role of FDA

When confronted with an emerging disease with significant public health impact:

• FDA provided expedited review of chemistry, manufacturing and controls (CMC) information, preclinical and clinical protocols, and clinical trials data, where available

• Numerous meetings with sponsors to discuss CMC issues, clinical development programs, and pathways to licensure for Ebola virus vaccines
Facilitating Ebola Vaccine Development - Role of FDA (cont.)

- International collaboration among regulatory agencies in review, with goal of regulatory convergence
- Participation in WHO organized joint reviews with African regulators
- Scientific workshop (Dec 2014) on Ebola virus and vaccine immunology
- FDA Vaccines Advisory Committee public meeting (May 2015) to discuss clinical development of Ebola vaccine candidates
Key Considerations for Ebola Vaccines

• Vaccine approval was based on validated and well-controlled manufacturing process
• Vaccine approval was based on adequate and well-controlled studies demonstrating safety and effectiveness
• Future Ebola vaccines have been/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 was/will be data-driven
Regulatory and Scientific Issues in Ebola Vaccine Development - Animal models

• Nonclinical studies: NHP models important
  • Provide initial safety data to support Phase 1 studies
  • Where applicable, the use of animal models can be important to understanding disease and mechanisms of protection
  • Support use of animal rule for licensure
  • However, vaccine doses that induce comparable immune responses may differ between humans and NHPs
Regulatory and Scientific Issues in Ebola Vaccine Development - Assays

- Critical to evaluate serology samples derived from pivotal trials using validated assays
  - For both human and NHP 9 (for animal rule) studies
- Assays for case ascertainment and immune response
  - Comparability of data across studies desired
  - Review of study data from multiple potential sponsors with concurrent clinical studies
  - Review of study data from multiple studies done with a single product
- Assay comparability, standardization, validation
  - Use of Master Files to facilitate information submission across multiple sponsors/products
Regulatory and Scientific Issues in Ebola 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
• Based on need to work towards licensure as quickly as possible:
  • Sponsor agreed to submit the following CMC information post-licensure as supplements to the BLA:
    • Final stability results for the ongoing studies of the DP PPQ lots
    • Updated operating targets and ranges for the manufacturing process
    • Data to support the total processing time for the final DP process
    • Final drug product validation report

• In an outbreak setting, the challenge was/is to keep pace with clinical development
Summary of Regulatory and Scientific Issues in Ebola Vaccine Development

- Multiple vaccine candidates
  - Parallel review of clinical studies for regulatory decision making
  - Communicating with different sponsors testing the same vaccines
  - Studies of a given vaccine may not have been conducted under oversight of the same regulatory authority, yet their outcomes needed to be considered in decision making
- Coordination of CMC and clinical development
- Pathways to licensure
  - Animal rule vs. clinical efficacy
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>
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<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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<tr>
<td>Animal Rule</td>
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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 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
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
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
Where did we utilize “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
Where will we continue to utilize “Lessons Learned”

- Reliance on prior knowledge – case by case/platform by platform basis
  - Reduced nonclinical safety testing requirements
    - Toxicology studies and in some cases biodistribution studies
    - Use of platform related stability data to support development
      - 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
  - At some level, yes
  - Critical human resource issue
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

Thank You