Lessons Learned from Ebola Vaccine Development Efforts

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Facilitating Ebola Vaccine Development

• Expedited review of chemistry, manufacturing and controls (CMC) information, preclinical and clinical protocols, and clinical trials data, where available, for Ebola vaccine candidates

• Numerous meetings with sponsors to discuss CMC issues, clinical development programs, and pathways to licensure for Ebola virus vaccines
Facilitating Ebola Vaccine Development (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
Pathways to Licensure

- Randomized, controlled trials that have clinical disease as the endpoint are the most robust study designs for demonstrating vaccine efficacy
- Other study designs and approaches may be appropriate
Licensure Pathways considered for Ebola Vaccines

• “Traditional” approval – based on protection against clinical disease or immune response, when there is a scientifically well-established marker of protection

• Accelerated approval: for products for serious or life-threatening illnesses providing meaningful benefit over existing treatments
  – Adequate and well-controlled clinical trials establishing an effect on a surrogate endpoint (e.g., immune response) reasonably likely to predict clinical benefit or a clinical endpoint other than survival or irreversible morbidity
  – Adequate and well-controlled studies required post-approval to verify clinical benefit
Licensure Pathways considered for Ebola Vaccines (cont.)

Animal rule approval: for products for serious or life-threatening conditions when human efficacy trials are not ethical or feasible, and approval based on other efficacy standards not possible

• May rely on adequate and well-controlled studies in animals to provide evidence of effectiveness when well-characterized animal model(s) for predicting response in humans are available

• Post-marketing studies to verify clinical benefit and to further assess safety required when such studies are feasible and ethical
Ebola Vaccines

• Ebola vaccines might be licensed based on
  – disease endpoint efficacy studies;
  – studies that show an effect on a surrogate marker *reasonably likely* to predict clinical benefit; or
  – animal studies

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

• Demonstration of pre-licensure clinical safety required for all pathways
Importance of Immunologic Assessments for Ebola Vaccines

• An immune marker reasonably likely to predict protection in vaccinees might be identified in a clinical study or through a combination of human and animal data

• Immune markers can be used to bridge between animals and humans under the animal rule

• Immunogenicity data important to support
  – Effectiveness in other settings (other age groups, manufacturing changes)
  – Clinical lot consistency
  – Dose selection
Regulatory and Scientific Issues in Ebola Vaccine Development

• Nonclinical studies: NHP models important to understanding mechanisms of protection; however, vaccine doses that induce comparable immune responses may differ between humans and NHPs and may need additional studies in some cases

• CMC issues
  – Product characterization and testing
  – Development of assays/methods
  – Other product considerations (e.g., stability, process validation, manufacturing consistency)
  – Challenge to keep pace with clinical development
Regulatory and Scientific Issues in Ebola Vaccine Development (cont.)

- Assays for case ascertainment and immune response
  - Comparability of data across studies desired
  - Assay comparability, standardization, validation
- Compressed clinical development: decision to proceed to advanced development based on interim data from earlier phase trials
Regulatory and Scientific Issues in Ebola Vaccine Development (cont.)

• Multiple vaccine candidates
  – Parallel review of clinical studies/overlapping studies for regulatory decision making
  – Communicating with different sponsors testing the same vaccines while maintaining confidentiality
  – Not all studies for a given vaccine may be conducted under oversight of the same regulatory authority, yet the outcomes of all studies need to be considered

• Pathways to licensure
• Post-marketing studies
• Communications
Key Considerations for Ebola Vaccines

• Vaccine approval is based on adequate and well-controlled studies demonstrating safety and effectiveness

• Ebola vaccines might be licensed based on
  – Disease endpoint efficacy studies;
  – Studies that show an effect on a surrogate marker (e.g., immune response) reasonably likely to predict clinical benefit; or
  – Animal studies

• The regulatory review of each vaccine will be data-driven and licensure pathways might differ
Key Considerations for Ebola Vaccines (cont.)

• CMC, assay development, and immune response evaluation are essential to successful vaccine development

• Continued engagement with stakeholders, e.g. vaccine manufacturers, clinical trial sponsors, national and international partners, is critical as well
How might these lessons apply to developing vaccines in response to other public health emergencies?

- General principles are applicable, e.g., expediting review, extensive interactions with vaccine manufacturers and other clinical trial sponsors, in-depth international collaborations among regulatory authorities and with WHO, academia, scientific community

- However, each disease and vaccine candidate has its own considerations

- Also, need to consider sustainability of efforts
Status of Ebola Vaccines at Time of 2014 Outbreak

- Ebola vaccine candidates were already under development and existing data allowed expedited entry into clinical trials
- NHP model available and provided important understanding regarding potential for vaccine candidates to protect
- Ebola virus disease: understanding of risk factors for exposure and high case fatality rate helped inform risk-benefit analysis for candidate vaccines
What is current status of Zika Vaccine Development?

• Just getting underway
• No validated animal models
• Other challenges
  – Most infections asymptomatic
  – Approximately 20% with mild disease
  – However, pregnant women at risk for transmission to fetus, with outcomes that include microcephaly or fetal loss
  – Risk to fetus greatest in first trimester, estimated between 1 and 13%
Other Challenges (cont.)

• Given risk in first trimester, need to protect women before they become pregnant
• What is appropriate target population?
• What is appropriate clinical endpoint to demonstrate efficacy and what assays are needed for case ascertainment?
• How will efficacy of vaccine in preventing microcephaly in future pregnancies be demonstrated?
• How does vaccination against or infection with other flaviviruses affect response to Zika vaccines?