FAST TRACK DEVELOPMENT OF EBOLA VACCINES: FDA REGULATORY PERSPECTIVE

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with Medical Countermeasures to Mitigate Risk of Emerging Infectious Diseases

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US FDA Activities to facilitate Ebola Vaccine Development

- Expedited review of CMC information, preclinical & clinical protocols and clinical trials data, where available, from clinical trials for Ebola vaccine candidates
- Approval of emergency use INDs for post-exposure prophylaxis
- Numerous meetings with sponsors to discuss CMC issues, clinical development programs and pathways to licensure for Ebola virus vaccines
- International collaboration in review, with goal of regulatory convergence
  - Multilateral t-cons with regulatory counterparts (e.g., EMA, HC)
  - Participation in WHO organized joint reviews with African regulators of Phase 2 and 3 clinical trial protocols for Ebola virus vaccines
- Co-sponsor of workshop (Dec 2014) on Ebola virus and vaccine immunology
  - Importance of immunological assessments for regulatory decision-making
- Planned meeting of OVRR's Vaccines and Related Biological Products Advisory Committee (VRBPAC) on clinical development of Ebola vaccine candidates
  - Regulatory approval may be based on outcome measures other than clinical disease endpoint(s)

Pathways to Licensure considered for Ebola Vaccines

- **"Traditional"** approval:
  - Protection against clinical disease (i.e., clinical disease endpoints)
  - Immunologic response, in some cases (i.e., scientifically well-established marker of protection)
- **Accelerated Approval:** for products for serious or life-threatening illnesses providing meaningful benefit over existing treatment (21 CFR 601.40/41)
  - For an Ebola vaccine, reliance on adequate and well-controlled clinical trials establishing an effect on a surrogate endpoint (e.g., immune response) that is *reasonably likely* to predict clinical benefit.
  - Adequate and well-controlled studies would be required post-licensure to verify clinical benefit
- **Animal Rule**: for products for certain serious or life-threatening conditions when human efficacy trials are not ethical or feasible, and approval based on other efficacy standards not possible (21 CFR 601.90/91)
  - Under specific conditions, when well-characterized animal model(s) for predicting response in humans are available, allows adequate and well-controlled studies in animals to provide evidence of effectiveness of the product
  - Post-marketing studies to verify the product's clinical benefit and to further assess safety must be conducted at a time when such studies are feasible and ethical.

- Demonstration of pre-licensure clinical safety required for all pathways

Importance of Immunological Assessments for Ebola Vaccines

- An immune marker *reasonably likely* to predict protection in vaccinees potentially could be identified in a clinical study or using a combination of human and animal data (and could be used to support accelerated approval)
- Immune markers can be used to bridge doses between animals & humans for approval under the animal rule
- Immune markers likely vaccine specific

- In addition, immunogenicity data also important to support:
  - effectiveness in other settings
    - e.g., use in additional age groups
    - e.g., manufacturing changes
  - clinical lot consistency
  - dose selection

Regulatory and Scientific Issues

Nonclinical studies

- Non-human primate (NHP) mimic human infections in important aspects and NHP studies are important for understanding mechanisms of protection; however, vaccine doses required to induce comparable immune responses may differ between humans and non-human primates
  - Need for additional studies with lead Ebola vaccine candidates in some cases

CMC issues

- Product characterization and testing
- Development of assays/methods
- Other product considerations (e.g., stability, process validation, manufacturing consistency, etc.)
- Challenge is to keep pace with clinical development

Assays for case ascertainment and immune response

- Comparability of data across studies desired
- Assay comparability/standardization/validation

Compressed clinical development

- Decision to support proceeding to advanced clinical development based on interim data from early phase clinical trials rather than data derived from final study reports

Regulatory and Scientific issues (cont.)

Multiple candidate vaccines

- Parallel review of clinical studies/overlapping studies for regulatory decision making
- Communicate with various sponsors using the same vaccines in the clinical studies but not manufacturing vaccine (maintaining confidentiality !)
- Many studies not conducted under US IND but their outcomes need to be considered in regulatory decision making

Pathways to licensure

- Consider existing alternative approaches to licensure if low or declining disease incidence or other factors lead to inconclusive phase 3 clinical disease endpoint trials
- Identification of immune markers to predict protection (may be vaccine specific)

Post-marketing studies

- Approval using the accelerated approval or animal rule provisions require studies to confirm clinical benefit
  - Design?
- Additional studies to further address safety may be needed

Communications

- Within FDA, sponsors, vaccine manufacturers, HHS, international partners

Summary Remarks

- FDA approves vaccines based on data derived from adequate and well controlled studies demonstrating the safety and effectiveness of the vaccines
- Ebola vaccines could be licensed based on clinical endpoint efficacy studies, studies that show an effect on a marker *reasonably likely* to predict clinical benefit, or animal studies
- Accelerated Approval and approval under the Animal Rule considered if Ebola infection rates do not permit direct assessment of efficacy in clinical trials, or for vaccines not being evaluated in current efficacy trials
- Immunological data, collected in ongoing and planned studies, will play an important role in vaccine evaluation and licensure
- Approval under the accelerated or animal rule provisions would require post-marketing studies to verify/confirm clinical benefit of the vaccines
- Continued engagement with stakeholders, e.g., vaccine manufacturers, clinical trial sponsors, national and international partners is critical for successful clinical development and licensure of Ebola vaccines