Regulatory Pathways for Licensure and Use of Ebola Virus Vaccines During the Current Outbreak
FDA Perspective

Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

WHO Consultation on Ebola Virus Vaccines
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Outline

• General Regulatory Considerations

• U.S. FDA Licensure Pathways

• Potential Approaches to Demonstrate Effectiveness of Ebola Virus Vaccines
  • “Traditional” Approval
  • Accelerated Approval

• U.S. FDA Expanded Access Regulations
General Regulatory Considerations
Phases of Vaccine Development under IND

- **Preclinical**
  - Safety
  - Immunogenicity
  - Dose Ranging
  - 20-80 subjects

- **Phase 1**
  - Safety
  - Immunogenicity
  - Dose Ranging
  - Generally hundreds of subjects

- **Phase 2**
  - Safety
  - Immunogenicity
  - Dose Ranging
  - Generally several thousand subjects

- **Phase 3**
  - Safety
  - Immunogenicity
  - Efficacy

Earlier Stages

Later Stages
Biologics Licensure

- Section 351 of the Public Health Service Act, 42 USC 262:
  The Secretary shall approve a biologics license application (BLA) - on the basis of a demonstration that –
  - the biological product ... is safe, pure, and potent; and
  - the facility ... meets standards designed to assure that the biological product continues to be safe, pure, and potent; ....

- Only those vaccines that are **demonstrated to be safe and effective**, and that can be **manufactured in a consistent manner** will be licensed by the FDA
Demonstration of Effectiveness of Preventive Vaccines

21 CFR 201.57: “...all indications [e.g., prevention of disease]...must be supported by substantial evidence of effectiveness.”

Expectation that demonstration of effectiveness is based on adequate and well-controlled clinical studies using a product that is standardized as to identity, strength, quality, purity and dosage form
Characteristics of Adequate and Well-Controlled Studies

- Pre-specified objectives and analysis methods
- Valid comparison with a control to provide a quantitative assessment of vaccine effect
- Method of assigning participants to study groups minimizes bias and helps assure comparability with regard to other pertinent variables
- Measures taken to minimize bias on the part of the subjects, observers, and analysis of data
- Methods of assessment of response are well-defined and reliable

See 21 CFR 314.126
Licensure Pathways

• “Traditional” Approval
• Accelerated Approval
• “Animal Rule”

Demonstration of clinical safety required for all pathways

Demonstration of effectiveness required for all pathways; differences in approach among pathways

Accelerated Approval and Animal Rule-- specific “eligibility” criteria and associated requirements
Safety Database Considerations

- Nature of the product
- Intended use
- Severity of the disease to be prevented
“Traditional” Approval

Pre-licensure clinical studies provide evidence of effectiveness based on:

• Protection against clinical disease
• Immunologic response, in some cases
  • scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
  • facilitated by an understanding of disease pathogenesis and mechanism by which vaccine prevents disease
Accelerated Approval

21 CFR 601.40 and 601.41

• **Scope:** Products studied for safety and effectiveness in treating serious or life-threatening disease or condition AND that provide meaningful therapeutic benefit over existing treatments

• Approval may be based on adequate, well-controlled clinical trials establishing an effect on a **surrogate endpoint that is reasonably likely...to predict clinical benefit**...

• **Requirement** to verify clinical benefit; required post-marketing studies:
  • usually underway at time of approval
  • must be adequate and well-controlled
  • must be conducted with due diligence
“Animal Rule”

21 CFR 601.90-91

• **Scope:**
  • Products that have been studied for safety and efficacy in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances
  • Human efficacy studies cannot be conducted:
    • unethical to deliberately expose healthy humans
    • field trials after accidental or hostile exposure not feasible

• **Not applicable if product can be approved based on other efficacy standards** (i.e. “traditional” approval or accelerated approval)
“Animal Rule” for Biological Products

21 CFR 601.90-91

Requirements to assure that animal studies establish reasonable likelihood of clinical benefit in humans, e.g.

• Pathophysiological mechanism of toxicity of the substance and prevention by the product well understood
• Effect shown in >1 species unless 1 model sufficiently well-characterized for predicting human response
• Animal endpoints clearly related to desired benefit in humans, generally improved survival or prevention of major morbidity
• Data allow selection of effective human dose

Requirement for post-marketing clinical studies to verify benefit and evaluate safety when such studies become ethical/feasible
Potential Approaches to Demonstrate Effectiveness of Ebola Virus Vaccines:

Traditional Approval Pathway
Accelerated Approval Pathway
Ebola Vaccines: Traditional Approval

- Effectiveness
  - An adequate and well controlled study conducted in an outbreak area to evaluate a clinical disease endpoint – typically such studies are randomized with a placebo or inactive control
  - May need immunogenicity data to “bridge” the immune response of outbreak area populations to non-outbreak area populations (e.g. U.S.)

- Considerations
  - Provides: the most rigorous scientific data, ethical and transparent allocation of limited investigational product to affected areas
• Considerations continued:
  • Feasibility of conducting a randomized controlled trial in outbreak area? e.g. Clinical trial infrastructure
  • Study size: depends on e.g. attack rate, endpoint (e.g. disease, infection)
Ebola Vaccines: Accelerated Approval

• Effectiveness
  • Randomized controlled trials conducted to evaluate an immunogenicity endpoint reasonably likely to predict protection (outbreak or similar population; non-outbreak population)
  • Adequate and well controlled post-marketing clinical study to confirm benefit

• Considerations
  • Need to identify a surrogate marker reasonably likely to predict protection (immunogenicity endpoint)
  • Design of the confirmatory study
Accelerated Approval: Considerations cont’d

• Current data needs: Identification of a surrogate marker reasonably likely to predict protection:
  • Data from NHP challenge studies w/candidate vaccines and Phase 1 human studies (Africa, US, EU)
    • Ebola virus neutralization titers?
    • Ebola virus glycoprotein antibody level?
  • Do we have enough information? E.g. seroprevalence information
• Consider assay feasibility (e.g. ELISA vs. CMI response measure) and assay capabilities (e.g. sensitivity, specificity, precision)
Expanded Access Regulations
(21 CFR 312 Subpart I)
Expanded Access to Investigational New Drugs

• Primary Purpose: To provide access to investigational drugs when there is no comparable or satisfactory alternative. Not to collect systematic safety or effectiveness data.
Expanded Access: Criteria to be met for all expanded access uses

• The disease or condition is “serious or immediately life threatening and there is no comparable or satisfactory alternative.”

• The “potential benefit justifies the potential risks... and those potential risks are not unreasonable in the context of the disease or condition... ; and”

• “Providing the investigational drug for the requested use will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the product for that expanded access use or otherwise compromise potential development of the expanded access use.” 312.305(a)
Expanded Access: Investigator Responsibilities

- Ensure:
  - Informed consent obtained
  - Institutional Review Board (IRB) review of expanded access use is obtained
- Report adverse events to the sponsor
- Record keeping (case histories and drug disposition records and record retention)
Licensure pathways for Ebola Virus vaccines are available:
  - Traditional Approval
  - Accelerated Approval

All pathways require evidence of safety and demonstration of effectiveness

Additional information required to determine most appropriate pathway

Expanded Access regulations permit use of an investigational vaccine in populations not enrolled in clinical studies provided certain conditions are met
Thank you.
EXTRA SLIDES
Categories of Expanded Access

- Individual patients, including for emergency use
- Intermediate-size patient populations
- Treatment IND or treatment population