Outline

• Clinical Development

• Considerations for vaccine development during public health emergency, e.g., Ebola

• Licensure Pathways

• Approaches to Make Unlicensed Vaccines Available
  ➢ IND, Expanded Access, Emergency Use Authorization

• Programs to facilitate product development

• Summary
Vaccines Against Emerging Infectious Diseases

Development follows same paradigm as other preventive vaccines; however, unique considerations apply if development occurs during a public health emergency.

- Preclinical Data (CMC/tox)
- Clinical data derived from human studies
- Stability data
- Facility Data
- Manufacturing Process
Development Strategy for Vaccines against Emerging Infectious Diseases

- 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
Examples of Emerging and re-emerging Infectious Diseases

- H1N1 (2009)
- MERS (2012)
- H7N9 (2013)
- Ebola (2014)
- Zika (2015)
Regulatory Framework to Make Vaccines Available

**Licensure**
- “Traditional” Approval
- Accelerated Approval
- “Animal Rule” Approval

**IND**
Unapproved product with no, or limited, human safety and effectiveness data
Expanded access use options

**EUA**
Unapproved product, or unapproved use of an approved product, in response to a public health emergency
Clinical Development of Vaccines for Licensure

Licensure pathways: “Traditional” Approval, Accelerated Approval, “Animal Rule” approval

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

Access mechanisms for unapproved vaccines

IND

Expanded Access

EUA
Primary Objectives of IND Review

21 CFR 312.22(a)

• In all phases of the investigation, to assure the safety and rights of subjects

• In Phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of effectiveness and safety
Phase 3 Clinical Trials of Preventive Vaccines

- Confirm clinical benefit (efficacy/immunogenicity)
- Expand knowledge of safety (including serious and less common adverse events)
- Randomized, controlled
- Often thousands or tens of thousands
  - Clinical endpoint efficacy trials usually provide a large safety database
  - When numbers of subjects included in efficacy trials or immunogenicity trials are insufficient to provide adequate safety data, additional controlled safety trials required
- Detailed surveillance and monitoring plans (safety and efficacy/immunogenicity)
Demonstration of Safety & Effectiveness of Preventive Vaccines

Effectiveness:

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

• 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.

Safety database considerations:

• Characteristics of the vaccine
• Safety signals or theoretical safety concerns
• Target population/ Intended use
• Seriousness of disease targeted for prevention
Considerations for Vaccine Development during Emergency Situations: Example - Ebola

• Ebola vaccine candidates were already under development and existing data allowed expedited entry into clinical trials
  • NHP model available
  • Ebola virus disease: understanding of risk factors for exposure and high case fatality rate helped inform risk-benefit analysis for candidate vaccines

• Larger phase 1 clinical studies to increase the early safety and immunogenicity database, facilitating timely initiation of Phase 2 clinical studies.

• Compressed timelines for clinical development by initiating Phase 3 studies based on interim safety and immunogenicity data from earlier phase studies
  • Disease epidemiology had major impact on the timing and design of Phase 3 studies.
  • Alternative trial designs, e.g., step-wedge

• Close collaboration between public health authorities, national regulatory agencies, the affected communities, clinical investigators, and vaccine developers essential to agree on development pathways
Clinical Trial Design Considerations for Ebola Vaccines

- 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 found to be appropriate, e.g., cluster-randomized trials
  - Step-wedge trial where the candidate vaccine is administered to predefined groups in a sequential fashion
  - Ring vaccination trial where the direct contacts of a case, and sometimes secondary contacts, may be randomized to vaccine or control or may be randomized to receive immediate vaccination or vaccination after a delay period
    - Increase statistical power by recruiting those at highest risk of infection (e.g., persons socially or geographically connected to an index case).
Product/CMC related Considerations for Ebola vaccines

• Product characterization and testing
  • Supportive data from platform-related products
• Specifications for some assays based on related products (e.g., 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 required
Regulatory and Scientific Issues in Ebola Vaccine Development: Assays

- Assays for case ascertainment and immune response
  - Comparability of data across studies desired
  - Assay comparability, standardization, validation
- Critical to evaluate serology samples derived from pivotal trials using validated assays
Regulatory Challenges in Ebola Vaccine Development

• 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
• Studies of a given vaccine may not be conducted under oversight of the same regulatory authority, yet their outcomes need to be considered in decision making
• Pathways to licensure tailored to specific product
Facilitating Ebola Vaccine Development
Role of FDA

• 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
How might these Lessons apply to developing Vaccines against Emerging Infectious Diseases?

• 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, and the scientific community

• Of note, each disease and vaccine candidate has unique considerations
How might these Lessons apply to developing Vaccines against Emerging Infectious Diseases?

Short time lines available for analytical development prior to initiation of pivotal studies
- Does not permit full validation of all assays
- Full validation of critical assays for safety
- Qualification of other characterization tests

Accelerated clinical development plan
- Adaptive clinical trial designs, e.g., nested Phase 1 & 2 trials incorporated into Phase 3 trial rather than separate studies
- Interim looks for efficacy
Key Considerations for Emerging Infectious Diseases Vaccines

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

- Emerging infectious diseases vaccines might be licensed based on demonstration of 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
  - Animal studies

- The regulatory review of each vaccine will be data-driven and licensure pathways might differ
U.S. Licensure Pathways

- Demonstration of clinical safety is required for all pathways.
- Demonstration of effectiveness is required for all pathways, there are differences in approach among pathways.
- *Accelerated Approval and Animal Rule have specific “eligibility” criteria and associated requirements.

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.
Licensure Pathways
“Traditional Approval”

“Traditional” Approval”

based on adequate and well-controlled clinical studies demonstrating:

- Prevention of disease or Immunologic response
  - 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

Considerations

- Feasibility of conducting an “outbreak” field trial
- Ethical considerations of randomizing to a placebo or inactive control.
- May need immunogenicity data to bridge non-outbreak area populations (traveler’s indication)
- Trial size will vary depending on attack rate, endpoint of interest (infection vs disease outcome), estimate of vaccine efficacy
Licensure Pathways (cont.)
“Accelerated Approval”

Accelerated Approval

- for product addressing serious or life-threatening illnesses AND provide meaningful therapeutic benefit over existing therapy
- adequate and well-controlled clinical trial using surrogate endpoint reasonably likely to predict clinical benefit; need to verify clinical benefit post-approval (21 CFR Subpart E, 601.41)

Considerations

- A surrogate endpoint needs to be identified
  - Based on animal and human data
  - Assay precision, validation and performance
- Confirmatory trial design
  - Adequate and well controlled in a post-licensure setting (may be ongoing a the time of approval)
Licensure Pathways (cont.)
“Animal Rule” Approval

**Animal Rule Approval**

- for serious or life-threatening conditions;
- definitive human efficacy studies not ethical or feasible;
- efficacy based on adequate and well-controlled animal studies;
- need to **verify** clinical benefit during exigency
- Not applicable to products that can be approved via “traditional” or accelerated approval pathways

*(21 CFR Subpart H, 601.90-95)*

**Considerations**

- Pathophysiological mechanism of toxicity of the substance and prevention by the product needs to be reasonably well understood
- >1 animal species that mimics human disease and response to vaccine (unless single species sufficiently well characterized)
- Animal endpoint clearly related to desired benefit in the humans
  - Improved survival
  - Prevention of major morbidity e.g. congenital malformations
Approaches to making unlicensed Vaccine against Emerging Infectious Diseases Available

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

IND

Expanded Access

EUA
Investigational New Drug Application (IND)

• 21 CFR 312
• Clinical investigations of an unapproved vaccine against an emerging infectious disease

• IND content includes:
  • Protocol for planned study(ies)
  • CMC information:
    • DS and DP: …acceptable limits and analytical methods to assure identity, strength, quality and purity; stability
  • Toxicology information
  • Sponsor and investigator responsibilities
Expanded Access to Investigational New Drugs

• Expanded Access Regulations
  (21 CFR 312 Subpart I)

Facilitate availability of investigational drugs to patients with serious or immediately life-threatening diseases or conditions when there is no comparable or satisfactory alternative

• Primary Purpose: To provide access to investigational drugs when there is no comparable or satisfactory alternative, not to collect systematic safety or effectiveness data
  • When patient enrollment in a clinical trial is not possible, patients may be able to receive a product, when appropriate, through expanded access.
Categories of Expanded Access

- Individual Patients
- Intermediate-size populations
- Treatment IND or treatment protocol (wide spread use)
The following criteria will need 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.

- Providing the investigational drug will not interfere with clinical development of the product for the expanded access use.
Expanded Access

Within each category, there are additional criteria to be met.

In general, there are increasing levels of evidence required for expanded access as the number of individuals to be treated increases, for example:

**Individual Patients**
- Probable risk to the person from the investigational drug is not greater than the probable risk from the disease.

**Intermediate Size**
- Evidence that the drug is safe at dose and duration proposed for use to justify a clinical trial
- Preliminary evidence of effectiveness

**Treatment Population**
- Clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence
- Actively pursuing marketing approval
Approaches to making unlicensed Vaccines against Emerging Infectious Diseases Available

- R&D
- Pre-clin
- Phase 1
- Phase 2
- Phase 3
- BLA
- Phase 4
- IND
- Expanded Access
- EUA
Emergency Use Authorization

• Declaration of an emergency or threat justifying emergency use…for a product on the basis of-

...a determination by the Secretary that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents;...
Emergency Use Authorization

• The following criteria apply to emergency use of a product
  – The agent can cause a serious or life-threatening disease or condition

  – Based on the totality of evidence…including from adequate and well controlled trials, if available, it is reasonable to believe that

    – The product **may be effective** in preventing such disease or condition

    – The **known and potential benefits of the use of the product outweigh the known and potential risks** of the product

    – There is **no adequate, approved, and available alternative to the product for preventing such disease or condition**
Emergency Use Authorization Considerations

• Informed consent is not required.
• To the extent practicable, recipients should be informed of the EUA, the known and potential benefits and risks…, and the option to accept or refuse and of any available alternatives.
• The product is expected to be manufactured in compliance with GMP.
Programs to Facilitate Product Development

• to facilitate and expedite the development of new drugs to address unmet medical needs in the treatment and prevention of a serious or life-threatening conditions

• Objective of programs is to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness
Programs to Facilitate Product Development

Accelerated Approval
• allows approval of a drug that demonstrates an effect on a “surrogate endpoint” that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

Priority review
• FDA’s goal to take action on a marketing application within 8 months of receipt instead of 12 months under standard review.

Fast track designation
• on the basis of preclinical data, more frequent interactions with FDA during drug development
Programs to Facilitate Product Development

Breakthrough therapy designation

• intended to expedite the development and review of drugs for serious or life-threatening conditions.

• requires preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.

• conveys all of the fast track program features

• provides for more intensive FDA guidance on an efficient drug development program as well as an organizational commitment involving FDA senior managers.

• A drug that has received a breakthrough therapy designation or a fast track designation may be eligible for priority review if supported by clinical and can be eligible for the accelerated approval pathway, if the relevant criteria are met.
Summary

• Emerging infectious diseases 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.
  • “Traditional” Approval
  • Accelerated Approval
  • Animal rule

• Regulatory mechanisms are available to permit access to investigational vaccines against emerging infectious diseases
  • IND/IND Expanded Access
  • Emergency Use Authorization

• Programs are available to facilitate product development

• Each vaccine candidate has unique considerations.
Continued engagement with stakeholders, i.e., vaccine manufacturers, clinical trial sponsors, national and international partners is critical for successful clinical development and licensure of vaccines against emerging infectious diseases.