Zika Virus Vaccines: FDA Perspective on Emergency Use and Accelerated Approval Process

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

WHO Consultation on Considerations for regulatory Expectations for Zika Vaccines for Use During an Emergency

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Regulatory Pathways to Make Zika Virus Vaccines Available

- Investigational New Drug Application (IND)
  - Unapproved product with no, or limited, human safety and effectiveness data
  - Expanded access option for individuals, intermediate size patient populations or wide-spread use

- Emergency Use Authorization (EUA)
  - Unapproved product, or unapproved use of an approved product, in response to a public health emergency or the potential for a public health emergency

- Biologics License Application (BLA)
  - “Traditional” Approval
  - Accelerated Approval
  - “Animal Rule”
Approaches to Make Unlicensed Zika Virus Vaccines Available:

- Investigational New Drug Application (IND)
- Emergency Use Authorization
Investigational New Drug Application (IND) 21 CFR 312

- Clinical investigations of an unapproved Zika virus vaccine

- IND content includes:
  - Protocol for planned study(ies)
  - CMC information:
    - DS: ... acceptable limits and analytical methods to assure identity, strength, quality and purity; stability
    - DP: ... acceptable limits and analytical methods to assure identity, strength, quality and purity; stability

- Toxicology information
IND Sponsor Responsibilities

Selected sponsor responsibilities:

- Selecting investigators
- Inform investigators of new safety observations wrt AEs and safe use
- Monitor progress of all investigations
- Review safety and effectiveness evidence
- Safety reporting to FDA
- Annual report to FDA
IND investigator responsibilities

Selected Investigator responsibilities:

- Informed consent of each subject
- Control of investigational drug
- Record keeping and record retention
- Progress reports to sponsor
- Report SAEs to sponsor
- Assure IRB review and approval of proposed study
- Compliance with 21 CFR part 50 (Protection of Human Subjects) and 56 (Institutional Review Boards)
Phases of Vaccine Development under IND

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

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

- **Phase 2**
  - Safety
  - Immunogenicity
  - Efficacy
  - Generally several thousand subjects

- **Phase 3**

**Earlier Stages**

**Later Stages**
Expanded Access Regulations
(21 CFR 312 Subpart I)
Expanded Access to Investigational New Drugs

To 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.
Categories of Expanded Access

- Individual patients, including for emergency use
- Intermediate-size patient populations
- Treatment IND or treatment population (wide spread use)
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...
- Providing the investigational drug will not interfere with clinical development of the product for that expanded access use
Expanded Access Use

Within each category, there are additional criteria that must 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:

- For individual use, the physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease.

FDA must determine that:

- There is enough evidence that the drug is safe at dose and duration proposed for expanded access use to justify a clinical trial in the approximate number of patients expected to receive the drug under expanded access.

- There is preliminary evidence of effectiveness, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable...option in the anticipated patient population.

Drug may or may not be under development for marketing for the expanded access use.
Expanded Access: Treatment IND or Treatment Protocol (1)

FDA must determine that:

- Drug is being investigated in a controlled clinical trial under IND designed to support a marketing application for the expanded access use (or all clinical trials have been completed)
- Sponsor is actively pursuing marketing approval
- For a serious disease or condition, sufficient clinical evidence of safety and effectiveness to support expanded access use, ordinarily from phase 3 trials, could be compelling data from phase 2 trials
- For immediately life-threatening disease, available evidence provides reasonable basis to conclude that investigational drug may be effective and would not expose patients to unreasonable and significant risk; such evidence ordinarily from phase 3 or 2 trials, but could be based on more preliminary clinical evidence
Expanded Access: Treatment IND or Treatment Protocol (2)

- For an immediately life threatening disease of condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.
Expanded Access Submission

- Submission can be a new IND or a new protocol to an existing IND
- Description of facility where vaccine will be manufactured
- CMC information adequate to ensure the proper identification, quality, purity and strength of the investigational product
- Pharm/toxicology information (adequate to support clinical testing of drug in population of the size expected to be treated)
- Sponsor and investigator responsibilities are as described for INDs
- Informed consent and IRB approval required
Emergency Use Authorization
(Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) of 2013)
Emergency Use Authorization (1)

• 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 (2)

• Criteria for issuance of authorization with respect to emergency use of a product only if ...
  – The agent can cause a serious or life-threatening disease or condition
  – That 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 (3)

• Other
  – Informed consent not required
  – To the extent practicable recipients should be informed of the EUA, the known and potential benefits and risks..., the option to accept or refuse and of any available alternatives
  – Product expected to be manufactured in compliance with GMP
Licensure
Section 351 PHS Act
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
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.
Safety Database Considerations

- Nature of the product
- Intended use
- Severity of the disease to be prevented
Pre-licensure clinical studies provide evidence of effectiveness based on:

- Protection against clinical disease (not limited to serious or life-threatening 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
Summary

- Regulatory mechanisms are available to permit use of investigational Zika virus vaccines
  - IND
  - IND Expanded Access Regulations
  - Emergency Use Authorization

- Licensure pathways require demonstration of safety and effectiveness
  - “Traditional” Approval
  - Accelerated Approval
Additional Information

Expanded access regulations:
21 CFR Sections 312.300, 312.305, 312.310, 312.315 and 312.320

Draft Guidance for Industry: Expanded Access to Investigational Drugs for Treatment use – Qs & As

FDA web page with information on access to investigational drugs outside of a clinical trial (expanded access):
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessstoInvestigationalDrugs/ucm176098.htm
Thank you!