U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products
Advisory Committee Meeting
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Approaches to Assessing Effectiveness of Chikungunya Vaccines

Sudhakar Agnihothram, Ph.D.
Office of Vaccines Research and Review
CBER/FDA/DHHS

Overview

- Regulatory Framework for Endpoints to Assess Vaccine Effectiveness
- Clinical Disease Endpoint Efficacy Trials
- Approaches to Identify an Immune Marker Reasonably Likely to Predict Protection from Chikungunya virus (CHIKV) Infection and Disease
  - Sero-epidemiological studies
  - Non-human primate (NHP) studies
- Topics For VRBPAC Discussion

Vaccine Effectiveness Endpoints In the Context of Approval Pathways

- "Traditional" approval pathway
  - Clinical disease endpoint or a biomarker (*e.g.*, immune response) scientifically established to predict protection against CHIKV infection and disease

- Other approval pathways (available for certain diseases/scenarios)
  - Accelerated approval: surrogate endpoint (*e.g.*, immune marker) reasonably likely to predict clinical benefit (protection against disease)
  - "Animal Rule" approval: disease endpoint in relevant animal model(s) and clinical studies to select an effective dose/regimen in humans
  - Both pathways require post-approval confirmatory studies

- Discussion of the most appropriate approval pathway is beyond the scope of this VRBPAC

Clinical Disease Endpoint Efficacy Trials

- In the absence of a scientifically established immune marker that predicts protection against CHIKV infection and disease, “traditional” approval would require a clinical disease endpoint efficacy trial
  - Ideally, a randomized controlled, double blind, trial to demonstrate vaccine effectiveness against virologically-confirmed CHIKV infection and disease
- Feasibility of field efficacy trials
  - Increased scope and frequency of Chikungunya outbreaks with high attack rates may allow for field efficacy trials of Chikungunya vaccines
  - However, outbreaks are irregular and unpredictable, and therefore feasibility of such trials is uncertain
  - Considerations for feasibility of field efficacy trials also include ensuring adequate infrastructure and close monitoring for Chikungunya disease activity

Approaches to Identify Immune Markers Reasonably Likely to Predict Protection Against CHIKV Infection and Disease

Sero-Epidemiological Studies

- Sero-epidemiological studies have been proposed as an approach to identify an immune marker reasonably likely to predict protection
- Prospective, sero-epidemiological studies in Chikungunya endemic regions could employ active surveillance and serologic/virologic testing methods to identify cases of CHIKV infection, with correlation of baseline antibody titers (*e.g.*, CHIKV-neutralizing antibodies) at enrollment with infection and disease outcomes during the surveillance period
- Considerations for sero-epidemiologic studies include:
  - Reliability of surveillance and testing methods to identify clinical cases that reflect established features of Chikungunya disease and epidemiology
  - Subject recruitment methods to avoid potential selection bias
  - Proper validation of serologic assays to quantify antibody titers
  - Measured immune marker may correlate with, but not be responsible for, protection against Chikungunya disease

Cynomolgus Macaque Model of CHIKV Infection and Disease

- A NHP model of CHIKV infection and disease has been proposed to identify an immune marker reasonably likely to predict protection in humans
- A cynomolgus macaque model recapitulates several features of human Chikungunya disease including fever, rash, viremia (tissue dissemination), and abnormal blood chemistry
- Uncertainties regarding the relevance of this model to human disease include:
  - Differences in disease features during subacute and chronic phase observed between cynomolgus macaques and humans
  - A challenge dose of CHIKV representative of natural infection in humans (10^3 PFU) induces fever, which may be accompanied by rash, but no overt signs of arthritis
  - Higher challenge doses (>10^7 PFU) of CHIKV induce inflammation and effusion in joints and results in meningoencephalitis and death in cynomolgus macaques

Passive Transfer of Human Antibodies to Non-Human Primates (NHPs)

- Passive transfer of pooled human sera or purified IgG from vaccinees into NHPs prior to CHIKV challenge has been proposed to identify an immune marker reasonably likely to predict protection
- Uncertainties regarding the utility of passive-transfer studies in NHPs include:
  - Will an immune marker derived using pooled human serum or purified IgGs (prepared from pooled serum) accurately predict protection from Chikungunya disease in humans?
  - Are there clinically meaningful differences in antibody quality that may influence protective capacity between a certain titer in a vaccinated human and the same titer resulting from dilution during passive transfer?
  - What would be the optimal timing for collecting post-vaccination human serum to be used in passive transfer studies?
  - Will other factors in human serum, besides antibodies (*e.g.*, cytokines), contribute to protection against CHIKV infection and disease?

Topics for VRBPAC Discussion

1. **Discuss the following aspects of clinical studies to assess effectiveness of CHIK vaccines:**

   – Feasibility of randomized, controlled clinical disease endpoint efficacy trials

   – Role of sero-epidemiologic data in identifying an immune marker reasonably likely to predict vaccine effectiveness

Topics For VRBPAC Discussion

2. **Discuss the utility of the non-human primate (NHP) challenge model to assess effectiveness of CHIK vaccines, including:**
   - Effectiveness endpoints, such as viremia, arthritis-related endpoints or other essential endpoints
   - Role of passively transferred sera or purified IgG from vaccinated humans in identifying an immune marker reasonably likely to predict vaccine effectiveness
   - Whether additional information is needed to support the utility of the NHP challenge model

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Thank you!