U.S. FOOD & DRUG ADMINISTRATION

Introduction

188th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

David C. Kaslow, M.D.
Director, Office of Vaccines Research and Review/CBER/FDA
12 December 2024

188th VRBPAC Meeting Topics

Topic I: Discuss Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations.

Topic II: Overview of Research Programs in the Laboratory of Immunoregulation (LI) and the Laboratory of Retroviruses (LR) in the Division of Viral Products (DVP | OVRR | CBER).

Topic I: Discuss Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations.

Current Context

- Observation in 1960's of enhanced respiratory disease (ERD) following RSV infection in formalin-inactivated RSV (FI-RSV) vaccinees cast a long shadow over RSV vaccine development.
- Recent advances in vaccine technologies and structural immunology, and plausible immune mechanisms that may explain FI-RSV vaccine-associated ERD (VAERD) facilitated RSV vaccine development and evaluation, respectively, including in adult, pregnant, and pediatric populations.
- Licensure of products that provide passive RSV immunity during infancy have partially addressed the unmet need for pediatric RSV vaccines.

New Considerations

- An imbalance in severe RSV lower respiratory tract disease has been observed following administration of mRNA-based RSV vaccine candidates to infants, the cause and mechanism of which have not been established.
- A potential RSV mAb – RSV vaccine interaction has been observed that may impact active immunization in infants and toddlers.

Topic I: Discuss Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations.

- CDC: Epidemiology of Respiratory Syncytial Virus in U.S. Children
  - Dr. Fatimah S. Dawood, CDC
- Clinical and Nonclinical Aspects of RSV Vaccine Safety in Young Children
  - Dr. Pedro A. Piedra, Baylor College of Medicine
- Review of Investigational RSV (mRNA-1345) and RSV/hMPV (mRNA-1365) Vaccines in Infants and Children < 2 Years
  - Drs. Christine Shaw and Matthew Snape, Moderna
- FDA: Imbalance in Severe Respiratory Syncytial Virus (RSV) Cases in a Clinical Trial of an RSV Vaccine in Infants and Young Children
  - Dr. Mark Connelly, FDA
- Open Public Hearing
- Committee Discussion and Recommendations

Topic I: Discuss Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations.

Discussion Topics

1. RSV Vaccine Safety in Pediatric Populations

1.1 Please discuss whether the currently available evidence indicates a potential safety concern more broadly applicable to the evaluation of RSV vaccine candidates in infants and toddlers. Please discuss the applicability to:

a. different vaccine technologies (e.g., live-attenuated RSV, viral-vectored, mRNA, and subunit protein vaccines); and

b. different antigenic conformations (e.g., stabilized preF or other RSV protein prototypes).

1.2 Based on the currently available evidence, please discuss current nonclinical and clinical safeguards, and recommend whether any additional nonclinical and clinical information should be considered and/or precautions taken when evaluating RSV vaccine candidates in infants and toddlers.

Topic I: Discuss Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations.

Discussion Topics

2. Sequential Administration of RSV Monoclonal Antibodies (mAbs) followed by RSV Vaccines in Infants and Toddlers

2.1 Please discuss whether currently available evidence suggests potential RSV mAb (e.g., nirsevimab) - RSV vaccine interactions that may affect active immunization in infants and toddlers.

2.2 Based on currently available evidence, please discuss and recommend whether any additional factors and data should be considered when evaluating RSV mAb - RSV vaccine interactions, including potential impact of administration of RSV mAbs on safety and/or effectiveness of subsequent parenteral or mucosal administration of RSV vaccines.

Considerations for Pediatric RSV Vaccine Development under U.S. IND

Considerations for enrollment of presumed RSV-naïve infants and children for RSV vaccine candidates under U.S. IND include:

1. If and how our current understanding of FI-RSV VAERD pathophysiology may inform benefit-risk assessments of other vaccine technologies
2. What critical additional assessments may further characterize the observed safety signal
3. What additional data may help stratify potential VAERD risk across vaccine technologies and antigenic compositions
4. How nonclinical studies may further inform potential VAERD risk in clinical studies
5. What additional risk mitigation/management strategies may address potential VAERD risk in clinical studies
6. How benefit-risk assessments may incorporate vaccine candidate benefits in RSV-experienced children, uncertainties regarding potential VAERD risk, and available preventative interventions (e.g., RSV mAb and maternal immunization)
7. How to address potential RSV mAb – RSV vaccine interactions in clinical development plans and pediatric clinical study designs


FDA
U.S. FOOD & DRUG
ADMINISTRATION