Regulatory considerations for RSV vaccine development

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The views expressed in this talk represent the views of the speaker and do not necessarily represent the views of FDA.
Vaccine development

**Pre-clinical**

- Safety
  - (~20-80)

**Phase 1**

- Safety
- Dose-Ranging, Efficacy
  - (100’s)

**Phase 2**

- Safety, Dose-Ranging, Efficacy
  - (100-1,000’s)
- Powered for hypothesis-testing

**Phase 3**

- Safety, Efficacy
  - (100-1,000’s)

**Phase 4**

- Approval
  - Post-Marketing
- Safety, Effectiveness
  - (»1,000’s)

**SAFETY**

- Effectiveness
- Manufacturing Consistency
- Clinical Assay Development
Biologics licensure

• Must demonstrate
  – the product is safe, pure and potent; and
  – the facility in which the biologic product is manufactured, processed, packed, or held meets standards designed to assure that the biologic product continues to be safe, pure and potent; ...

• Only those biologics 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

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
RSV vaccine target populations

- **Maternal immunization**: 0 – 6 months

- **Direct immunization**
  - Infants
  - Older adults
    - Immunocompromised at high risk, e.g. HSCT patients

- **Indirect effects** potentially beyond vaccinated populations
Pathways for licensure of biologics

- **“Traditional”** approval – safety, purity and potency shown by non-clinical studies, full description of manufacture methods and facilities, lot release tests, labels, containers and adequate and well-controlled clinical trial(s)
  - Although it depends on the target population, this is the likely pathway for a new RSV vaccine, because randomized, blinded, controlled trials with a clinical disease endpoint (which could support traditional approval) should be feasible, given the incidence of RSV disease.

- **Accelerated** approval – same as above except for serious or life-threatening illnesses and adequate and well-controlled clinical trial using **surrogate endpoint** reasonably likely to predict clinical benefit; need to verify clinical benefit post-approval

- **Animal Rule** – same as above except for serious or life-threatening conditions; definitive human efficacy studies not feasible; efficacy based on animal studies; need to verify clinical benefit post-approval
Begin with the goal in mind.

Goal: To develop human safety and effectiveness data adequate to support the proposed indication and intended use.
Target Product Profile Guidance for Industry

• Ideal version of what the sponsor would like to claim in labeling

• Guides the design, conduct, and analysis of clinical trials

• Supports a structured dialogue to reach an understanding of the FDA’s thinking on various aspects of a development program

RSV vaccines in development

• Live attenuated
• Whole Inactivated
• Particle based
• Subunit
• Nucleic Acid
• Gene-based Vectors
• Other type and prime-boost
• Novel adjuvants
Demonstration of safety, pre-clinical

- Based on class of vaccine, indicated population and manufacturing process
- For other than live-attenuated vaccines:
  - Show no enhanced disease in vaccinated animals after infection with wt RSV
  - Multiple animal models of vaccine-enhanced disease in RSV-naïve infants
- Toxicology study for:
  - non-replicating vaccines
  - vaccines with novel adjuvants
- Pre-clinical data necessary to support studies in humans will be evaluated on a case by case basis
Clinical safety pre-licensure

• Characterize reactogenicity and common AE’s related to vaccine

• Assess relatively rare vaccine-related AE’s

• Evaluate in adults and seropositive children before RSV-naïve infants*

• Novel adjuvant may require larger pre-licensure safety database

*Importance of early discussion with FDA regarding necessary pre-clinical studies before 1st human study, and before study in RSV-naïve infants
Demonstration of efficacy

- Pre-specify and validate case definition (P1 and P2)

- Dose selection, e.g. including adjuvant (P2)

- Validated clinical assays; evaluate correlate of protection (CoP) in P3

*Agreed upon with FDA at EOP2*
**Demonstration of efficacy (cont)**

- Double-blind, randomized, placebo-controlled RCT for P₃ study(ies)
- Selection of P₃ efficacy endpoint(s)* based on indication(s) and target population sought
  - Prevention of disease: symptomatic, medically attended, lower respiratory, hospitalization
  - Case definition: composite of clinical + laboratory
  - Recommend testing for RSV (PCR or antigen) in all cases of suspected RSV, regardless of severity
- Secondary endpoints may include:
  - Coinfection with other respiratory viruses (e.g., influenza, rhinovirus, etc)
  - Comorbid outcomes, such as bacterial pneumonia, otitis media

*Agreed upon with FDA at EOP2*
Sample size estimates for efficacy trials

These calculations assume a significance level of $p=0.05$.

In contrast, CBER typically recommends that sample size calculations start with a point estimate of efficacy, and rule out a 95% confidence interval lower bound of $\frac{1}{2}$ to $2/3$ of the point estimate. In the example above, the recommended approach would result in larger sample size estimates.
Maternal immunization

• Currently there are no licensed vaccines with an indication specifically for use in pregnant women to prevent disease in the infant

• Such a vaccine should meet the same criteria for safety in the vaccinated population, i.e. pregnant women, effectiveness and manufacturing consistency for FDA licensure

• More complex framework for safety and effectiveness applicable to both mother and infants

• FDA’s Office of Vaccines recently published a review of the regulatory considerations regarding clinical development of vaccines indicated for use in pregnancy*

Clinical development of preventive vaccines for use in pregnancy: pre-licensure studies

- **Phase 1 study**
  - Non-pregnant women of childbearing potential
  - Safety

- **Phase 2 study**
  - Non-pregnant women of childbearing potential
  - Safety & Immunogenicity

- **Phase 1 study**
  - Pregnant women “low risk”
  - Safety

- **Phase 2 study**
  - Pregnant women
  - Safety & Immunogenicity

- **Phase 3 study**
  - Pregnant women
  - Efficacy & Safety

- **Post-Licensure study(s)**
  - pregnant women

* Preclinical reproductive toxicity study recommended at or before this step.
Size of safety database to support licensure for use in pregnancy

- Capacity to detect a small magnitude of increased relative risk of rare unanticipated adverse outcomes is limited, even with a relatively large sample size

- Prelicensure clinical studies to detect rare adverse events (e.g., neurocognitive adverse outcomes or individual congenital anomalies) not anticipated

- Sponsors are expected to consider the overall benefit-risk assessment and provide reasonable assurance that benefits outweigh the risks with regard to rare adverse outcomes

- Product dependent
Size of Safety Database (cont)

Pre-licensure safety database for licensed infant vaccines:

- Varivax  (1995) 8,000  Rotarix  (2008) 36,000
- Rotateq  (2006) 36,000  MenHibrix(2012) 7,000

• Expectations for the size of the safety database* are typically discussed at the end of phase 2 (EOP2) meeting. Some of the factors considered include:
  • review of the safety data accrued to date
  • the need to further characterize known safety signals or theoretical safety issues
  • anticipated use of the vaccine (e.g., for the entire birth cohort?)
  • initial benefit risk assessment, based on target population, disease prevented, indication for use, etc.

*# of subjects vaccinated with the final formulation, dose, and regimen
Pregnancy and Lactation Labeling Rule (PLLRL) – Implications for Maternal Vaccination

• Evaluate current labeling to ensure it accurately reflects current knowledge about use of the product during pregnancy; need to update label when new information becomes available
  • Removes letter categories (i.e. A, B, C, X)
  • Consider product-specific data from animal studies, clinical trials, pregnancy exposure registries, observational postlicensure studies, case series, etc

• Licensed vaccines recommended by public health advisory bodies (e.g., influenza, TdaP)
  • No anticipated impact on existing recommendations
  • No requirement for additional studies

• Investigational vaccines being developed for use in pregnancy
  • No impact on requirement for substantial evidence of effectiveness and demonstration of safety
  • No impact on expectations for adequate and well-controlled studies
Foreign Studies

• If the expectation is that the study will be used to support licensure by FDA, then the sponsor is encouraged to conduct the study under IND.

• FDA has accepted non-IND studies to support licensure if the studies are conducted according to ICH standards.*

• In these circumstances, a clinical bridging study may be necessary to provide scientific support for the safety and effectiveness of the vaccine when administered to pregnant women in the U.S.

*Other criteria that must be met are discussed in regulations (e.g., 21 CFR 312.120) and guidance (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf).
Summary

• Infants < 6m immune response to RSV is poor and is likely age-related resulting in high disease burden
• Inactivated vaccine has caused enhanced disease in RSV-naive infants
• In order for other than live-attenuated new vaccines to be evaluated in RSV-naïve infants risk must be shown to be acceptable
• Passively transferred antibody is protective suggesting that a maternal immunization strategy could be effective
Summary (cont)

• Maternal immunization presents a complex benefit-risk framework for evaluation of vaccines that has to take into account both mother and infants
• There are still many gaps in our knowledge of the pathogenesis, relevance of animal models and the immune system’s response to RSV natural infection and vaccines
• FDA is prepared to work with the RSV community and manufacturers to develop vaccines that can be licensed to address this significant public health need.
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