FDA Perspective: Safety Evaluation of Preventive Vaccines

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

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Overview

• Preventive vaccines: Pre-licensure safety evaluation
• Preventive vaccines: Post-licensure safety evaluation
  – Surveillance for GBS after vaccination with Influenza A (H1N1) 2009
• Selected target population considerations
  – Pregnant women
Regulatory Definition of Safety

21 CFR 600.3

“relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time”
Safety Considerations for Preventive Zika Vaccines

Safety “in relation to the condition of the recipient. . .”

• Target population: generally healthy people (Proposed Zika TPP: females of child-bearing age)

• Potential inclusion in national vaccination programs (concomitant vaccines)

...expect low tolerance for vaccine-associated risks
Key Events in Vaccine Development

Pre-IND

- Develop rationale
- Identify Immunogen
- Develop manufacturing process
- Non-clinical studies

IND

- General investigational plan
- Phase 1
- Phase 2
- Phase 3
- BLA
- Postmarketing

Licensing

Phase 4

IND: Investigational New Drug Application
BLA: Biologics License Application
Pre-licensure Safety Evaluation
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)
Phase 3 Safety Evaluation of Preventive Vaccines: Statistical Considerations

• Analyses usually exploratory in nature
  – Few *a priori* hypotheses, but many analyses

• No statistical adjustment for multiple testing
  – Failure to identify true safety signal more critical error than detecting a false signal

• Some trials may aim to test specific hypothesis regarding a potential vaccine-associated adverse event
Considerations regarding the size of safety database to support licensure

• Expectations for the size of the safety database typically discussed at end of phase 2 or earlier.
• Factors considered include:
  • characteristics of the vaccine
  • review of early phase safety data
  • any safety signals or theoretical safety issues
  • target population
  • seriousness of disease targeted for prevention
• For preventive vaccines, the size of the safety database is typically on the order of several thousands

*# of subjects vaccinated with the final formulation, dose, and regimen
Licensing Phase

• Biologics License Application (BLA)
  – contains product and manufacturing information and data from nonclinical and clinical studies to demonstrate safety, purity, and potency

• Multidisciplinary FDA review committee
  – medical, product, assay, manufacturing facility, statistical, epidemiology, toxicology, labeling, other consultants as needed

• FDA advisory committee review
  – provide opinion regarding adequacy of safety and efficacy data

• FDA decision
  – benefit-risk assessment
Post-licensure Safety Evaluation
Postmarketing Monitoring of Vaccine Safety- Why?

• To further characterize the safety profile of licensed vaccines
  – Pre licensure clinical trials may not detect safety issues that arise when products are marketed to the general population

• To maintain an outcomes focused “warning system” for production problems
  – Monitor patterns by lot
Selected Postmarketing Safety Activities

• Routine pharmacovigilance
  – Vaccine Adverse Event Reporting System
  – Global pharmacovigilance (sponsors, public health agencies, regulators)

• Post-marketing commitment safety studies - e.g., to monitor for rare events; pregnancy registries

• Required post-marketing safety studies and trials
  – If FDA becomes aware of certain new safety information about serious risks related to use of a drug

• Post-licensure Rapid Immunization Safety Surveillance System
  – active electronic safety monitoring
  – FDA partners with holders of automated healthcare data
  – Data on over 100 million persons
Surveillance for Guillain-Barré Syndrome after vaccination with Influenza A (H1N1) 2009
Guillain-Barré Syndrome (GBS) following influenza vaccine - historical data

- Immune-mediated acute demyelinating polyneuropathy affecting the peripheral nervous system
- Estimated annual incidence rate: 1 case per 100,000 population
- In 1976, a type of influenza vaccine was causally associated with GBS*  
  – 1 additional case per 100,000 persons vaccinated
- Subsequent studies of influenza vaccines suggest that if there is any risk for GBS after seasonal influenza vaccines, it is very small, on the order of about one in a million.

* Institute of Medicine, 2004
# Influenza A (H1N1) 2009 Vaccines U.S. Safety Monitoring Activities

<table>
<thead>
<tr>
<th>System</th>
<th>Sponsor</th>
<th># subjects</th>
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<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC/FDA</td>
<td>passive</td>
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<tr>
<td>Vaccine Safety Data Link (VSD)</td>
<td>CDC</td>
<td>~9.5 million</td>
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<tr>
<td>Centers for Medicare &amp; Medicaid Services Databases</td>
<td>CMS</td>
<td>~38 million</td>
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<tr>
<td>Post-Licensure Rapid Immunization Safety Monitoring (PRISM)</td>
<td>NVPO, FDA &amp; CDC</td>
<td>~30 million</td>
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<tr>
<td>Dept of Veterans Affairs Databases</td>
<td>VA</td>
<td>~1.2 million</td>
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<tr>
<td>Defense Medical Surveillance System (DMSS)</td>
<td>DoD</td>
<td>~1.4 million</td>
</tr>
<tr>
<td>Indian Health Service Resource and Patient Management Database</td>
<td>IHS</td>
<td>~1.4 million</td>
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<tr>
<td>Vaccines &amp; Medications in Pregnancy Surveillance System (VAMPSS)</td>
<td>BARDA</td>
<td>~2400</td>
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<td>Clinical Immunization Safety Assessment (CISA)</td>
<td>CDC</td>
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<tr>
<td><strong>Emerging Infections Program (EIP), (GBS case-finding)</strong></td>
<td>CDC</td>
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<tr>
<td>Real-Time Immunization Monitoring System (RTIMS)</td>
<td>CDC</td>
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GBS surveillance – meta-analysis

• CDC Emerging Infections Program, Medicare, Vaccine Safety datalink, PRISM*, Dept. of Defense, Dept. of Veterans Affairs
  – Salmon et al., The Lancet, 2013
  – ~23 million persons vaccinated with influenza A (H1N1) monovalent vaccine
  – Self controlled study design
  – Approximately 1.6 excess cases of GBS per million people vaccinated

*Post- Licensure Rapid Immunization Safety Monitoring (PRISM)
Considerations for Vaccination of Pregnant Women
A potential approach to clinical development of a vaccine intended for use in pregnancy to protect the young infant (Nov. 2015 VRBPAC)

- **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
  - **Effectiveness & Safety**

- Post-Licensure study(s)
  - pregnant women

* Preclinical reproductive toxicity study should be done at or before this step.
Considerations for the collection of safety data to monitor for unanticipated risks

• Pregnancy and neonatal outcomes data collected as part of routine prenatal care
• Serious adverse events
• New onset medical conditions in the mother
• Infant outcomes data; consider including developmental assessments
• Power to detect rare adverse outcomes is based on the size of the safety database
Considerations for safety evaluation of vaccines intended for use in pregnancy

• Complications of pregnancy (i.e., adverse outcomes) are common, even among pregnancies identified as “low risk” and rates vary substantially in different populations.
  – Example: preterm birth occurs in ~5% of pregnancies in EU countries and up to 18% in Sub-Saharan Africa

• Important to determine background rate in study population
  – For safety monitoring during the study; and
  – To enhance interpretation of study data
Maternal immunization – practical support for clinical development

• **NIH sponsored workshop series** to improve the design and conduct of maternal immunization studies – publications:

• **WHO/Brighton initiative** to develop standard case definitions of key outcomes in pregnancy for monitoring and evaluation during maternal immunization studies*

• **FDA**:
  – Workshop on postlicensure registries/studies in pregnant women: [http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm](http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm)

Thank-you!