Assessing the Safety of Vaccines at the FDA: Pre- and Post-Licensure Evaluation

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Outline

- Legal framework
- Pre-licensure safety evaluation
  - Investigational New Drug (IND) Application Process
  - Biologics License Application (BLA) Process
- Post-licensure safety evaluation
- Illustrative examples

Scope: Preventive vaccines against infectious diseases
FDA Legal Framework

Statutes
(enacted by Congress, signed by President)

→

Regulations
(FDA)
Main Statutes Pertinent to Vaccine Safety

- Federal Food, Drug and Cosmetic Act
- Public Health Service Act
- FDA Amendments Act
US Code of Federal Regulations (CFR)

FDA implements statutes through regulations

- 21 CFR 600-680 Biological Product Standards
- 21 CFR 314.126 Adequate and well-controlled trials
- 21 CFR 312 Investigational New Drug Application
- 21 CFR 210-211 Good Manufacturing Practices
- 21 CFR 58 Good Laboratory Practices
- 21 CFR 56 Institutional Review Boards
- 21 CFR 50 Protection of Human Subjects
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”
Unique Safety Considerations for Preventive Vaccines

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

- Target population: millions of healthy people, including young infants and children, each year
- State governments mandate many vaccines for children attending public schools or day care centers
- Individual risk for disease prevented by vaccination may be low (e.g., diphtheria, polio)

...thus, low tolerance for vaccine-associated risks

- FDA requires new vaccines to be studied in the context of concomitant use with other recommended vaccines that are given on the same, or overlapping, schedule
Pre-licensure Safety Evaluation
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

Licensing

BLA

Postmarketing

Phase 4

IND: Investigational New Drug Application
BLA: Biologics License Application
Investigational New Drug (IND) Application

21 CFR 312

ISTR IND application must contain:

- Manufacturing and product information
- Non-clinical pharmacology and toxicology data
- Summary of previous human experience
- Clinical protocols and investigator information

ISTR FDA may impose an order to delay a proposed clinical
study (or halt an ongoing study) based on specified
regulatory criteria, including unreasonable and significant
risk to human subjects
Stages of Vaccine Review and Regulation

Clinical Investigational Plan

Phase 1 → Phase 2 → Phase 3 → BLA Data to support approval → Post-marketing Phase 4

Phase 1: Safety
Immuno-genicity

Phase 2: Immuno-genicity
Safety
Dose-ranging

Phase 3: Efficacy
Safety
Immuno-genicity

IND: Investigational New Drug Application
BLA: Biologics License Application
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 1 Clinical Trials of Preventive Vaccines

- Preliminary evaluation of safety and immunogenicity
- Design depends on pre-clinical data, experience with similar products
  - Often open label
  - Randomized, controlled in some cases
  - Dose escalation, in some cases
- Population
  - Small number of subjects (e.g., 20-80)
  - Adults usually studied before children
  - Inclusion/exclusion criteria to minimize risk
- Close, active safety monitoring (e.g., clinic visits, diary cards, case report forms), short- and long-term
  - (also for phase 2 and 3)
- Conservative stopping rules for safety
Phase 2 Clinical Trials of Preventive Vaccines

- Evaluation of safety (common local and systemic reactions) and immunogenicity
  - Dose ranging (some studies)
- Up to several hundred subjects per trial
- Usually randomized and controlled
- Entry criteria less restrictive, reflect target population
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 2 and 3 Clinical Trials of Preventive Vaccines

- New vaccines are evaluated in the context of the current recommended immunization schedule
  - Safety of concomitant immunization
  - Efficacy/immunogenicity of investigational vaccine administered concomitantly with other recommended vaccines
  - Interference in responses to other vaccines when administered with investigational vaccine (some studies)
Phase 3 Safety Evaluation of Preventive Vaccines: Statistical Considerations

- Analyses usually exploratory in nature
  - Few \textit{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
Stages of Vaccine Review and Regulation

Clinical Investigational Plan

↓  IND  ↓

Phase 1 → Phase 2 → Phase 3 → BLA
Safety → Immuno- → Efficacy → Data to support approval
Immunogenicity → Safety → Safety → approval
Safety → Immunogenicity → Immuno- → Post-
Dose- → genicity → marketing
ranging →

IND: Investigational New Drug Application
BLA: Biologics License Application
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-to-risk ratio considered.
Post-licensure Safety Evaluation
Postmarketing Adverse Event Reporting Requirements for Vaccine Manufacturers

21 CFR 600.80

* Manufacturer must report to FDA:
  * Serious and unexpected adverse experiences within 15 days
  * Other adverse experiences, quarterly for first 3 years after licensure, then annually
Regulatory Definitions  
(21 CFR 600.80)

**Serious adverse experience**

β “Any adverse experience . . . that results in . . . Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect” -or-

β “. . . based upon appropriate medical judgment, . . . may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed. . .”

**Unexpected adverse experience**

β “Any adverse experience that is not listed in current labeling for the biological product.”
Clinical Postmarketing Commitments

- Studies conducted by manufacturer to further evaluate safety (e.g., rare adverse events) or effectiveness (e.g. duration of vaccine-induced immunity)
- Agreed upon by FDA and manufacturer prior to approval
- Progress of studies monitored by FDA
FDA Amendments Act of 2007, Title IX Sec 901
Clinical Postmarketing Requirements

- Authorizes FDA to require postmarketing studies or clinical trials
  - at time of approval
  - post-approval if FDA becomes aware of new safety information
- FDA may consider safety information from clinical trials, adverse event reports, postmarketing studies, biomedical literature, other appropriate scientific data
- New authorities for monitoring and enforcement
Vaccine Adverse Event Reporting System (VAERS)

- National passive postmarketing vaccine safety surveillance system
- Established in 1990
- Co-administered by FDA and CDC
- Accepts reports from health care providers and the public
- Rapid detection of potential signals; hypothesis generating
- Limitations- reporting biases, missing data/inaccuracies, lack of controls, lack of information on number of persons vaccinated, inability to assess causality
FDA Amendments Act of 2007, Title IX Sec 905
Enhanced Postmarketing Safety Surveillance

Mandate for FDA to develop an enhanced ability to monitor the safety of drugs (including vaccines) in postmarketing setting
FDA’s *Sentinel Initiative*

- National electronic system for risk identification and analysis, linking safety data from multiple sources (academic medical centers, healthcare systems, health insurance companies)
- Active surveillance system designed to investigate safety questions in a timely manner
- Launched in 2008
- Met goal to access data from 25 million people by July 2010
- Goal to access data from 100 million people by July 2012
- Augments passive safety surveillance systems
Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Component of FDA’s pilot Sentinel Initiative that is dedicated to vaccine safety
- Launched in 2009 for pandemic influenza H1N1 vaccine safety surveillance
- Ongoing activities to assess possible association between:
  - intussusception and currently licensed rotavirus vaccines
  - venous thromboembolism and Gardasil (Human Papillomavirus Quadrivalent Vaccine)
Examples
Example of Vaccination Schedule in Pre-licensure Clinical Trials: Prevnar 13

<table>
<thead>
<tr>
<th>Study Vaccines</th>
<th>Age (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>PCV13 or PCV7</td>
<td>+</td>
</tr>
<tr>
<td>DTaP-HBV-IPV</td>
<td>+</td>
</tr>
<tr>
<td>Hib Conjugate</td>
<td>+</td>
</tr>
<tr>
<td>MMR and Varicella</td>
<td></td>
</tr>
</tbody>
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*Permissive use of hepatitis A vaccine, rotavirus vaccine and influenza vaccine in some studies

PCV7: Pneumococcal 7-valent conjugate vaccine (Prevnar)
Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (1)

Prevnar (pneumococcal 7-valent conjugate vaccine) (US licensure 2000)

- Safety experience derived primarily from efficacy trial
- ~18,000 infants received ~58,000 doses of Prevnar; similar number of infants in control group
- Common adverse events monitored by telephone interviews in ~3,000 infants in each group
- Relatively rare events requiring medical attention evaluated across all doses in all study participants using automated databases
Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (2)
Pentacel (DTaP-IPV-Hib) (US licensure 2008)

- Substantial previous experience with same manufacturer’s DTaP and Hib conjugate vaccines
- Nearly 6,000 study participants received at least one dose of Pentacel; most received four doses in controlled clinical trials (safety and immunogenicity)
Pre-Licensure Safety Database for Some Infant/Childhood Vaccines (3)

Rotarix (Rotavirus Vaccine, Live, Oral) (US licensure 2008)

- Increased risk of intussusception had been observed following administration of another manufacturer’s rotavirus vaccine (no longer licensed in US)

- Risk of intussusception with Rotarix evaluated in a pre-licensure safety trial including ~63,000 infants (no increased risk of intussusception observed following Rotarix compared with placebo)
Clinical Postmarketing Commitments to Expand Knowledge of Safety Profile- Examples

**Menveo** (meningococcal groups A, C, Y, W-135 conjugate vaccine)- initial US licensure Feb 2010 for use in persons 11 through 55 years of age

- Observational study in at least 50,000 vaccinated persons 11 through 19 years of age in a Health Maintenance Organization

**Prevnar 13** (pneumococcal 13-valent conjugate vaccine)- initial US licensure Feb 2010 for use in children 6 weeks through 5 years of age

- Observational study in at least 43,000 infants who receive all three infant series doses in a Health Maintenance Organization
Postmarketing Study Required under FDA Amendments Act of 2007- Example

Rotarix (Rotavirus Vaccine, Live, Oral)- US licensure 2008 for use in infants 6 weeks to 24 weeks of age

- Serious risk of intussusception associated with another live, oral rotavirus vaccine (no longer licensed in US)

Manufacturer required to conduct a postmarketing observational study of Rotarix to assess the potential risk of intussusception

- ~44,000 vaccinated infants (dependent on background rate of intussusception)

- Timetable for conduct/completion of study specified
Postmarketing Study Required under FDA Amendments Act of 2007- Example

Cervarix – vaccine against human papillomavirus licensed in 2009; currently approved for use in females 9 through 25 years of age

Safety signal: subgroup analysis of clinical trial data suggested imbalance in spontaneous abortions among Cervarix recipients whose pregnancies occurred around the time of vaccination compared to control subjects.

Manufacturer required to conduct epidemiologic study to assess risk of spontaneous abortion following Cervarix, according to specified timetable
Detection of Potential Safety Signal by VAERS and Follow-up Study

Menactra (meningococcal groups A, C, Y, and W-135 conjugate vaccine) licensed Jan 2005

- March 2005 - Sept 2006, 17 cases of Guillain-Barre Syndrome (GBS) within 6 weeks after Menactra reported to VAERS

- US retrospective cohort study using healthcare claims data from 9,578,688 adolescents to evaluate GBS risk following Menactra
  - 72 medical chart-confirmed GBS cases-- none had received Menactra within 42 days prior to symptom onset
  - Insufficient medical information for additional 129 potential cases

- Taking into account missing data, estimates of attributable risk of GBS range from 0 to 5 additional cases per 1,000,000 vaccinees within 6 weeks after vaccination

- Dec 2011: Menactra prescribing information updated with study results
FDA Vaccine Safety Assessment is Multifaceted

- Manufacturing processes
- Manufacturing facilities
- Product characterization
- Animal studies
- Pre-licensure clinical trials
- Post-licensure evaluation
- Concomitant immunization