Vaccine Safety: An FDA Perspective

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Educational Objectives

- Describe the major components of FDA's evaluation of a biologics license application for a preventive vaccine
- Discuss the sources of data that FDA uses to monitor vaccine safety after licensure
- Describe interactions between FDA and other governmental agencies in vaccine safety and other vaccine-related activities

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What is a Vaccine?

- Preventive vaccines
  - Intended to prevent infectious diseases by inducing a protective immune response
  - May contain all or a portion of the disease-causing or related organism or nucleic acid encoding 1 or more proteins from the organism
- Therapeutic vaccines
  - Intended to treat infectious diseases (e.g., HIV) or other diseases (e.g., cancer)

Examples of Licensed Vaccines

- Live, attenuated: MMR, varicella, yellow fever, influenza, rotavirus
- Inactivated: Hepatitis A, influenza, polio, rabies
- Crude or purified antigens derived from living or killed cells: diphtheria and tetanus toxoids, polysaccharides
- Conjugates: Hemophilus type b, pneumococcal, meningococcal
- Recombinant DNA derived: Hepatitis B, human papillomavirus

Vaccine Production: Challenges

- Biologic sources of viral or bacterial seed, cell substrate, other components
  - Test for adventitious agents
  - For inactivated vaccines, validate inactivation process
  - For live vaccines, demonstrate attenuating characteristics retained
- Complex manufacturing processes: detailed procedures, in process testing, product characterization, lot release testing all critical for consistency and quality of product

Clinical Lifecycle of a Vaccine

- Investigational new drug application
  - Phase 1: safety, immunogenicity
  - Phase 2: safety, immunogenicity, dose-ranging
  - Phase 3: safety, efficacy, immunogenicity
- Biologics license application
  - Review of safety, efficacy, manufacturing data
  - Conduct pre-approval inspection
  - Review pharmacovigilance plan
  - Usually obtain advice from FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC)
- Post-licensure
  - Phase 4 studies
  - Vaccine Adverse Event Reporting System (passive)
  - Lot release
  - Biennial inspections

Safety Database at Licensure

- Typically several thousand to tens of thousands of individuals
- Size may be influenced by
  - rare disease endpoint (e.g., invasive pneumococcal disease)
  - safety concern raised by related products (e.g., intussusception with first licensed rotavirus vaccine)
  - substantial experience with licensed components of combination vaccine, etc.

Safety Expectations

- Vaccines are expected to be very safe
- Consider that a routinely recommended childhood vaccine will be administered to
  - ~4 million children per birth cohort per year
  - Predominantly healthy
  - Vulnerable population
  - Vaccination often required by States (e.g., for school attendance)
- Expectations may change over time
  - e.g., as risk of vaccine-preventable disease decreases

Sample Sizes Needed in Clinical Trials to Detect Increases in Rates of Rare Events After Vaccination

Rates (%)	Sample Size*	No. Potentially Affected/year**
0.1 vs. 0.2	50,000	4,000
0.01 vs. 0.02	500,000	400

*Two-arm, power=80%, alpha (2 sided)=5%

**Assumes vaccine administered to birth cohort of 4 million

Adapted from Ellenberg SS, Safety considerations for new vaccine development. Pharmacoepidemiol Drug Saf. 2001 Aug-Sep;10(5):411-5.

Post-Licensure Vaccine Safety Monitoring

- International Conference on Harmonization: E2E Pharmacovigilance planning (PvP)
- PvP reviewed as part of BLA
- Vaccine safety monitored through
  - Vaccine Adverse Event Reporting System (VAERS)
  - Phase 4 studies may be part of post-licensure commitment

What is VAERS?

- National system for passive surveillance of adverse events after vaccination established in 1990 in response to National Childhood Vaccine Injury Act of 1986
- Jointly managed by FDA and CDC
- Reports received from health professionals, vaccine manufacturers, the public

Uses of VAERS

- Detecting unrecognized adverse events
- Monitoring known reactions
- Identifying possible risk factors
- Vaccine lot surveillance
- Comprehensive review of all data prior to regulatory action

Limitations of VAERS

- Reported diagnoses not verified
- Lack of consistent diagnostic criteria
- Wide range of data quality
- Underreporting
- Inadequate denominator data
- No unvaccinated control group
- Usually not possible to assess whether vaccine caused the reported adverse event

CDC Vaccine Safety Surveillance Resources

- Vaccine Safety Datalink: has 8 sites with computerized databases, includes ~3% of population
  - FDA coordinates with CDC and manufacturers so that phase 4 studies are complementary
- Brighton Collaboration for standardized case definitions of AEs following immunization
- Clinical Immunization Safety Assessment Centers

FDA and CDC Interactions

- FDA and CDC work together closely on vaccine safety surveillance activities, e.g. VAERS, VSD, analysis and communication of safety concerns
- CDC representative usually participates in FDA's Vaccines Advisory Committee (VRBPAC)
- FDA has ex-officio member on CDC's Advisory Committee on Immunization Practices (ACIP)
- VRBPAC typically provides advice regarding the safety and effectiveness of vaccine being considered for licensure
- ACIP makes recommendations for use of licensed vaccines

National Childhood Vaccine Injury Act (NCVIA), 1986

- Addressed vaccine liability concerns
  - Intent to ensure adequate supply of vaccines through the establishment of an accessible and efficient means to compensate individuals found to be injured by certain vaccines
- Mandated Federal vaccine safety infrastructure
  - National Vaccine Injury Compensation Program
    - Administered by HRSA
    - Compensation funded by vaccine excise tax
    - Limited to vaccines routinely recommended for children by CDC's ACIP

NCVIA (cont)

- National Vaccine Program Office
  - Coordinates vaccine and immunization activities among Federal agencies, including FDA, CDC, NIH, HRSA
- Vaccine Information Statements (CDC)
- IOM committee to review literature on vaccine AEs
- VAERS (FDA and CDC)
  - Act mandates that healthcare providers report certain AEs (AEs listed on VICP's vaccine injury table or listed as contraindications)

FDA and RedBook Interactions

- RedBook: Report of the American Academy of Pediatrics' (AAP) Committee on Infectious Diseases (COID)
- FDA liaison attends twice yearly COID meetings and provides updates on
  - New vaccine approvals
  - Upcoming AC meetings, FDA-sponsored workshop, and other publicly available information of interest
- FDA liaison does not participate in COID voting or policy making
- New RedBook published every 3 years
  - FDA reviewers may provide input prior to publication

A Case Study: Rotavirus Vaccine and Intussusception (IS)

- Rotashield: Pre-licensure data for IS
  - 5 cases in 10,054 vaccinees (0.05%)
  - 1 case in 4633 placebo recipients (0.022%)
  - Difference in rates not statistically significant
  - Lack of apparent association between IS and wild-type rotavirus infection*
- Phase 4 study commitment at licensure
- Licensed 8/98, for prevention of rotavirus gastroenteritis in infants
- Package insert: IS included as potential adverse reaction
- IS prospectively included as term in VAERS database

*Rennels et al., Pediatr Infect Dis J 1998;17:924-5.

Case Study (cont.)

- VAERS reports 9/1/98 – 6/2/99: 10 IS cases, temporal clustering after 1st dose and within 7 days after vaccination provided signal
- CDC initiated multi-state case-control study and cohort study in 10 MCOs in June 1999
- July 1999*
  - 15 IS cases reported to VAERS, 12 within 7 days after vaccination
    - Background rate in infants <1 yr, 51/100,000 infant years
    - ~1.5 million doses administered 8/98-6/1/99
    - 14-16 cases would be expected in week after vaccination by chance alone
  - Population-based studies suggested higher IS rates after vaccination (not statistically significant)
  - CDC and AAP recommended temporary suspension of use

*MMWR July 16, 1999; 48:577-581

Case Study (cont.)

- October 1999
  - Population-based studies: elevated risk of intussusception after vaccination*
  - ACIP withdrew its recommendation for vaccination
  - Wyeth voluntarily withdrew vaccine
- What was attributable risk?
  - Initial estimate 1/2500 to1/5000
  - Consensus estimate ~1/10,000**
- Did vaccine “trigger IS but result in no net increase?***

*MMWR September 3, 2004;53:786-789

**Pediatrics 2002;110:e67-73

***Lancet 2004;363:1547-50

How did this impact next rotavirus vaccine?

- Large pre-licensure safety study of Rotateq started in 2001, with input from VRBPAC (70,000 infants, 1:1 vaccine vs. placebo)
- For the pre-specified 42-day post-vaccination endpoint, 6 cases of IS observed in vaccine group vs. 5 cases of IS in the placebo group
- RR of 1.6 (95% CI, 0.4-6.4) (after adjustment for group sequential design)
- No increased risk of IS at day 42 post-vaccination compared to placebo
- No clustering of IT cases within 7 or 14 day window post-vaccination.

Rotateq

- Licensed 2/06 for prevention of rotavirus gastroenteritis in infants
- Passive surveillance using VAERS (Vaccine Adverse Event Reporting System)
  - Includes accelerated reporting of adverse events
  - Subject to limitations of passive surveillance systems
- Phase 4 study (44,000 infants)
- Vaccine Safety Datalink (VSD) study (90,000 infants)
- Regular coordination conference calls FDA-CDC-Manufacturers
- To date, no signal of increased risk of IS with Rotateq*

*MMWR March 16, 2007;56:218-222

Case Study: Meningococcal Conjugate Vaccine and GBS

- Menactra licensed 1/05 for prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 in ages 11-55 years
- Guillain-Barre syndrome (GBS): no cases seen in ~7,000 vaccinees in pre-licensure clinical trials
  - 5 cases reported to VAERS by 9/05, occurring within 6 weeks after vaccination and triggering concern re potential safety signal

Case Study (cont.)

- Rapid investigation, communication, with cooperation and information sharing among FDA, CDC, manufacturer, and public transparency
  - 9/05: FDA and CDC issued alert of ongoing investigation and encouraged reporting to VAERS*
  - 10/05: package insert revised to reflect temporal association between vaccination and GBS
  - 10/05, 4/06, 10/06: MMWR updates
  - 10/06 FDA/CDC statement** and MMWR***: uncertain but possible GBS risk of ~1 case/million doses
- Challenges: uncertainties in background rates, VAERS reporting, number of doses given, etc.
- 10/06: ACIP reaffirms its recommendations for routine immunization of adolescents

*http://www.fda.gov/bbs/topics/NEWS/2005/NEW01238.html

** http://www.fda.gov/cber/safety/gbs102006.htm

*** October 20, 2006;55:1120-1124

Case Study (cont.)

- Ongoing studies of GBS after Menactra
  - VSD: as of 11/17/07, no cases within 6 wks after vaccination among 228,003 11-19 year-olds (0.35 expected)
  - Harvard Pilgrim in conjunction with manufacturer, sanofi pasteur
    - Include 10 million 11-18 year-olds
    - Time period of 3/05 to 8/08
    - ~ 90% power to detect risk ratio of 3; 50% power to detect risk ratio of 2

FDA Efforts to Enhance Vaccine Safety

- Multi-disciplinary vaccine safety team (epidemiologists, clinical/product reviewers, compliance/manufacturing experts, communications) to improve acquisition, analysis, and communication of safety information
  - Encompasses entire life-cycle and all data relevant to safety, manufacturing, compliance
  - Uses data to evaluate emerging safety issues
  - Coordinates FDA response to emerging safety issues with other HHS agencies (CDC, NVPO, NIH), industry
  - Proactive: develop research, policy, outreach agendas
  - Enhances collaboration with other govt. agencies, WHO, and others on vaccine safety initiatives

Lessons Learned

- Pre-licensure clinical, product, and manufacturing data are critical foundations for evaluating the safety and effectiveness of vaccines
- However, post-licensure monitoring is essential to ensure vaccine safety
- Vaccines have real risks that may include rare serious adverse events that are not detected in pre-licensure studies
- Government agencies play an important role in monitoring, analyzing, and communicating re vaccine safety

Lessons Learned (cont.)

- Surveillance and observational studies after licensure are needed to detect and evaluate vaccine safety concerns
- Need for robust continuously operating and technologically advanced safety monitoring systems that include epidemiological, clinical, and laboratory assessments of causality
- Public communication and engagement regarding vaccine safety concerns is critical to maintaining confidence in the vaccine safety system, optimal vaccine coverage, and the public health

Thanks!

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