Vaccine Safety and Risk Management Update

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DIA Contemporary Pharmacovigilance and RMS
January 14, 2007

Disclaimer

- This presentation represents the views of the presenter and are not necessarily the views of the Food and Drug Administration or the U.S. Government.

Contents

- What is happening in vaccine safety?
- Premarket
- Postmarket
- New Actions
- FDAAA 2007
- Conclusions

Evolving Safety Expectations Includes Vaccines

- Changing expectations of FDA and industry
- Success of disease prevention increases expectation of safety
- New technologies utilizing different cell substrate systems and scrutiny over vaccine constituents
- New adjuvants proposed for wide population use
- Effects of vaccines investigated beyond disease prevention

Changing Safety Expectations for Vaccines

- “FDA is FDA and all medicines are DRUGS.”
- Risk Communication
  - More benefit/risk information (more is better)
  - Speed
  - Pediatric studies under PREA must be labeled
- Negative information on efficacy in public domain
- What is value-added efficacy or improved safety?
- What is in my child’s vaccine?

Evolving Benefits Expectations: Successes lead to Challenges

- Examples of successes
  - Small pox
  - D/T/P
  - Haemophilus influenzae b
- Examples of risks
  - GBS
  - Intussusception
- Unexpected, unusual risks
- Me-Toos

New Technologies and Constituents in Vaccines

- Cell substrates may offer advantages of more rapid, reliable, reproducible production
- Adventitious agents present concerns for safety and purity → necessitate thorough testing
- Preservatives and stabilizers
- Adjuvants-mechanism of action is not understood, enhance immune response
  - induction of Th1 and cytotoxic T lymphocyte responses /Toll-like receptor

New Adjuvants

- Aluminum and Alum
- Adjuvants enhance immune response: apply rational medical therapy
- What are all the tissue targets for adjuvants? What are the cascade effects?
- Do the new target populations present unique risk concerns?
- Desirable to have more than one presentation of a vaccine–adjuvanted and unadjuvanted?

Ideas About Pre-market Best Practices

- Non-clinical studies
- Dose-ranging studies
- Rational medical approach for combined products
- Re-examine exclusion criteria in Phase 3
- Team focus on collection of efficacy data commensurate with collection of safety concerns
- Pediatric development plans

Ideas about Pre-Market Best Practices--continued

- Long term safety
- Safety analyses
  - Types of events
  - Time to event(s) analyses
  - Novel agents—novel thinking
  - Attention, tools, resources
- Clear and upfront presentation of data
- Open communications/FDA/Industry

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.

Ideas About Post-market Best Practices

- Pharmacovigilance Plans for all BLAs
- Developing cooperative active surveillance systems
- Postmarketing studies to detect rare SAE, study use of the product
- How are products used in real world—safe?
- Pregnancy information
- Concomitant administration
- Evolving regimens and schedules, boosting

Ideas About Post-marketing Best Practices---continued

- Constant vigilance in manufacturing QA/QC, advances
- Supply and shortage anticipations
- Adding more and more value to product
- PLR labeling
- Clear and open communications
  - FDA-Manufacturer
  - Inside the manufacturer

New Actions: Vaccine Safety Team

- Newly formed in 2007
- Multi-disciplinary CBER Team
  - Bob Ball, Flo Houn, and Carmen Collazo
- OBE/OVRR Lead to integrate pre and postmarketing
- Rapid response, data and policy needs
- Gaps in Vaccine Safety in CBER
  - Pre and Post Marketing
  - Decision-making
  - Scientific Gaps

New Actions: RiskMAP and Subpart E 601.42 Approval

- Smallpox vaccinia vaccine, Live
- RiskMAP Goals and Objectives
  - Education for vaccinees and vaccine providers to achieve
    - Vaccine is administered safely and effectively
    - Vaccinees informed of risks and benefits
      - Myo-pericarditis, transmission, autoinoculation
    - Risks of transmission and autoinoc are minimized
- This RiskMAP is broad, not prescriptive
    - Process control is not lynchpin for safety
    - Approaches will differ for specific risks/controls

New Actions: RiskMAP continued

- Conditions of use in approval letter for national emergency declared by the Sec. of HHS
  - "In the event of an actual emergency, declared by the Secretary under Section 319 of the PHS Act, the conditions of use for the vaccine would change, altering the vaccine's risk/benefit balance. Consequently, the postmarketing restrictions needed to assure safe use would change accordingly…alternative approaches that meet the RiskMAP Goals and Objectives may be immediately implemented…"
- Outcomes-based RMP
- Evaluation is via outcomes of interest
  - Rates of transmission vaccinia, autoinoculation, and eczema vaccinatum

New Actions: Med Guide and PMC

- Yes, a medication guide can be mandated for vaccines.
- PMC
  - Active Surveillance and Enhanced Surveillance
  - Registry to learn about risk factors

New Actions: Labeling is the corner stone of risk management

- **WARNINGS AND PRECAUTIONS----------**

  Do not administer FluMist to children <24 months because of increased risk of hospitalization and wheezing observed in clinical trials. (5.1)

- **8.6 Use in Individuals 50-64 Years of Age**

  FluMist is not indicated for use in individuals 50-64 years of age. In Study AV009, effectiveness was not demonstrated in individuals 50-64 years of age (n=641). Solicited adverse events were similar in type and frequency to those reported in younger adults.

- **INDICATIONS AND USAGE---------**

  FLUVIRIN is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group. (8.4)

New Actions: Labeling--continued

- ACIP recommendations vs. FDA approved labeling
- Use of published literature
  - **Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products**
- Changing from “old” labeling to PLR

FDAAA 2007 Safety Mandates

- PREA
  - Assessments
  - Plans
  - Labeling
- Safety Labeling Changes for new safety info
- REMS
- Postmarketing Risk Assessment

FDAAA 2007 Safety-- continued

- Clinical Trials Databases
- Advisory Committee, Action Memos
- Risk Benefit Communication
- Priority Review for Tropical Disease
  - Different benefit/risk assessment

Conclusions

- Vaccines are given to healthy persons.
- Certain immunizations are mandated.
- Pre- and Post-licensure safety program
- All drugs have risks.
- FDA and manufacturers bear great responsibility in ensuring benefits of vaccination exceed risks.