Overview of Vaccine Safety Monitoring

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Agenda

- Introduction
- Risk Management
  - Definition
  - RM throughout development
  - Risk Management Plans
- Post-licensure Safety Surveillance
  - Passive Surveillance Systems
  - Post-licensure Studies
- Summary and Discussion

Product Safety

As we know, there are known knowns.
There are things we know we know.

We also know, there are known unknowns.
That is to say,we know there are some things we do not know.

But there are also unknown unknowns.
The ones we don't know we don't know.

~ Donald H. Rumsfeld, Feb. 12, 2002, Department of Defense news briefing

THE UNIVERSAL BLACK BOX WARNING??

This drug poses both known and unknown risks. Some of these risks may be severe and even result in death. The known risks are described in this product label. The unknown risks are still unknown.

Product Safety

- Risk is inherent
  - Failure to acknowledge this fact contributes to complacency and increases risk
- The acquisition of knowledge about the risks and safety of a drug product should continue throughout its life cycle.
- Proactive risk management by manufacturers has major benefits for patients, health care professionals, regulators and the manufacturers themselves.

Some Sources of Safety Data

- Clinical Trial Data
  - Most scientifically rigorous
  - Relatively small dataset
  - May not entirely reflect real world use
- Post-licensure voluntary reporting
  - Primary strength is detection of rare and serious events
  - No denominator
  - Subject to bias
- Epidemiologic studies
  - Many different designs
  - Often provide a comparison group
  - Objective may be signal identification or verification

Vaccine Risk Management

Risk Management

- Acknowledges that risk is inherent
- Risk assessment and risk minimization
  - Proactive approach is required to minimize the potential risks
- Continually evolving process
  - New data
  - Changes in disease state/treatment options shift risk/benefit balance
  - Periodic reassessment required

Risk Management Plans (RMP)

- RMPs are often required for new products and for certain other significant submissions
- Formal document which summarizes risk information and the plan to manage risks and to refine risk profile going forward
- The RMP summarizes the safety/risk data for the product and outlines safety-related actions to address them

RMP Structure

- Safety specification
  - Important identified risks
  - Important potential risks
  - Important missing information
- Pharmacovigilance plan
  - Must address each of the important identified and potential risks
- Risk minimization plan
  - Assess need for risk minimization
  - Not all product require risk minimization plan

Vaccine RMPs

- Tailored to the vaccine and the indicated population
- Common considerations
  - Adverse events/general safety
  - Duration of effect/need for booster
  - Effect on the disease ecology
    - Type replacement
  - Use with other vaccines

Vaccine RMPs

- Common actions
  - Routine pharmacovigilance
  - Enhanced PV
    - Examples include additional follow-up methods, registries
  - Safety surveillance studies
  - Effectiveness studies
  - Risk communication & benefit/risk education

Post-licensure Surveillance Systems

Passive Surveillance Systems

- Health care professionals or consumers voluntarily report illness after receipt of medicinal product
- Reports are non-standardized descriptions of symptoms/signs
- Reporting is encouraged whether or not the medicine is thought to be causal

Uses of Passive Surveillance Systems

- Signal generation
- Detection of unrecognized adverse events
  - Primary strength is detection of rare events
- Monitoring known reactions
- Identifying possible risk factors
- Vaccine lot surveillance

Limitations of Passive Reporting Systems

- Data quality issues
  - Incomplete, unverified, no consistent diagnostic criteria
- Bias
  - Rare & serious events more likely to be reported
  - Prompting
  - Weber effect/uptake period
- Difficult to put into context
    - Numerator subject to underreporting
    - Denominator estimated by doses distributed
    - No control or comparison group
- Cannot determine causality

Manufacturer's Passive Surveillance Systems

- Manufacturers collect spontaneously reported AEs
  - Data reported to regulators around the world
  - Monitored continuously and analyzed regularly
- Merck database
  - Contains spontaneous marketed reports, serious reports from clinical trials, reports from the literature
  - Worldwide
  - Events entered using reporter terminology and coded using a standard dictionary (MedDRA)

Brief Outline of Signal Detection

- Spontaneous reports monitored by trained health care professionals as they come in
- Periodic aggregate review by safety teams
  - More frequent for newer products or as needed
- Addition of automated signal detection methods
- Preparation of formal safety reports/analyses (e.g. Periodic Safety Update Reports)
- Signal investigation and further actions as appropriate

U.S. Vaccine Surveillance

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Clinical Immunization Safety Assessment Network (CISA)

Vaccine Adverse Event Reporting System (VAERS)

- US passive surveillance system for AEs after vaccination with US licensed products
- Jointly managed by CDC and FDA
- Emphasis is on US reports
- Includes reports from manufacturers (through FDA), from HCPs, and from consumers

Vaccine Safety Datalink

- Collaboration between CDC and 8 managed care organizations (MCOs)
- Large linked database
  - Vaccination data
  - Medical outcomes (outpatient and ED visits, hospitalizations)
  - Birth data
  - Census data
- Conducts population-based research into vaccine safety questions
- Rapid Cycle Analysis

CISA

- Network of 6 research centers with vaccine expertise
- Goals
  - To study pathophysiologic basis for AEs including the role of individual variation
  - To study risk factors for specific AEs after vaccination
  - To provide evidence-based guidelines on vaccination, revaccination & evaluation of AEs

Other Tools for Safety Surveillance

Epidemiologic Studies

- Many designs available
  - Signal detection or signal investigation possible
- Some common examples
  - Claims databases with medical record access
  - Large managed care databases with MR access (e.g. VSD)
  - Registries
  - Case-control studies

Brighton Collaboration

- International voluntary organization to facilitate high quality safety information about vaccines
- Committed to develop standardized, globally accepted case definitions for AEFI
  - Not diagnostic criteria
- Develop guidelines for data collection, analysis, and presentation

Summary

Summary

- Risk is inherent and can be mitigated, but not eliminated
- The acquisition of knowledge about the risks and safety of a drug product should continue throughout its life cycle.
- There are many sources of data about product safety
  - Research should continue into newer sources and methods

Summary

- Manufacturers, regulators, HCPs, and patients benefit from robust product safety infrastructure
- All the stakeholders must work together in order to improve the system