

Postmarket Safety Surveillance Principles, Tools, and Methods

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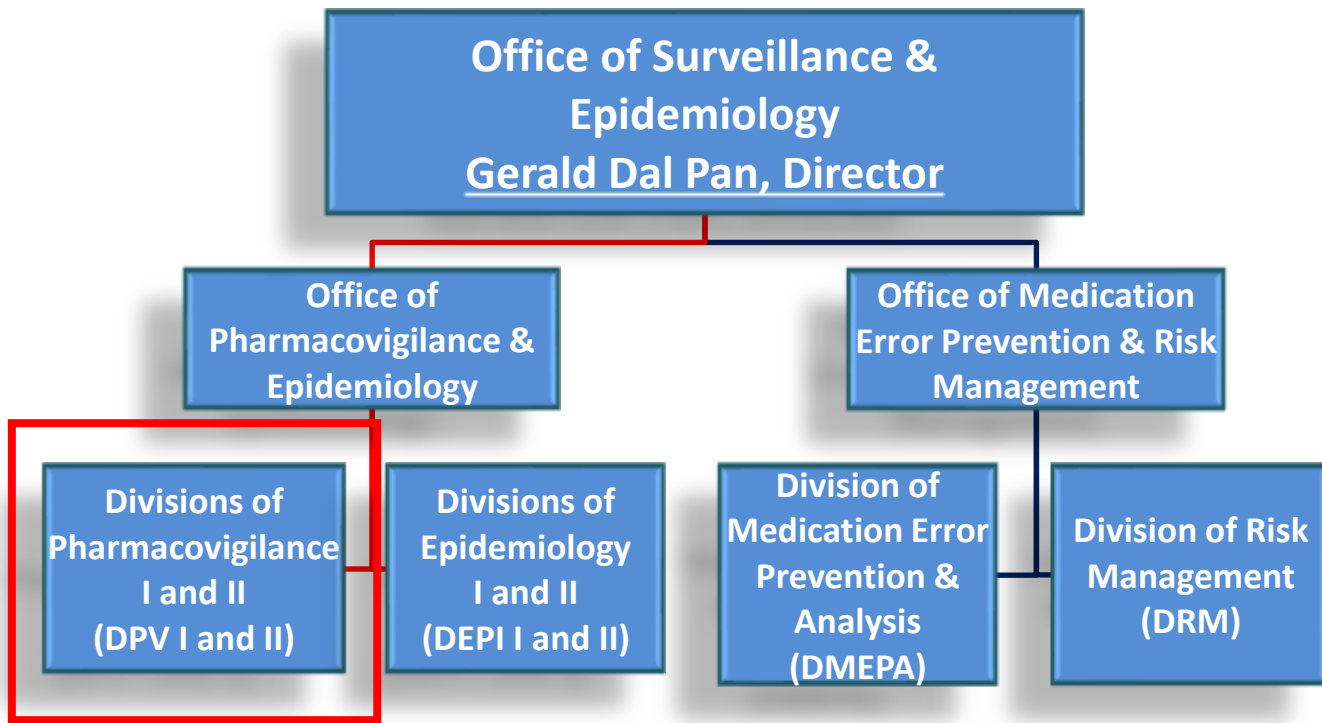
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Learning Objectives

- Describe the phases of postmarket safety surveillance
- Explain the principles of postmarket safety surveillance
- Understand the risk-based approach
- Discuss available data sources, tools, and methods

Abbreviation	Term
AE	Adverse Event
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
DPV	Division of Pharmacovigilance
FAERS	FDA Adverse Event Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
ICSR	Individual Case Safety Report
NEISS-CADES	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NISS	Newly Identified Safety Signal
NPDS	National Poison Data System
PHS Act	Public Health Service Act
PREA	Pediatric Research Equity Act
PSR	Periodic Safety Report
REMS	Risk Evaluation and Mitigation Strategy

Scope of Monitoring

- Products referenced under section 3075 of the 21st Century Cures Act*
 - Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act
 - Section 351 of the Public Health Service (PHS) Act
- Over-the-counter monograph products
- Compounded products
- Homeopathic products
- Other unapproved products

*The Act was enacted on December 13, 2016, and has the goal of advancing medical product innovation, as well as ensuring patient access to safe and effective treatments as soon as possible.

Phases of Postmarket Safety Surveillance



- Identify safety signals
- Triage and prioritize safety signals
- Evaluate safety signals
- Take regulatory actions
- Communicate safety information

Principles of Postmarket Safety Surveillance

- Multidisciplinary, life-cycle approach
- Use multiple/all available data sources
- Risk-based approach



Principles: Multidisciplinary, Life-cycle Approach

- Participate in pre-approval activities
 - Provide postmarket safety information if the product under evaluation is marketed outside of US
 - Understand safety information identified during drug development program
 - Plan for postmarket safety surveillance

Principles:

Use Multiple Data Sources



Data sources for ongoing surveillance

- FDA Adverse Event Reporting System (FAERS)
- Medical literature
- Periodic Safety Reports (PSR)

Principles:

Use Multiple Data Sources (cont'd)

Additional data sources

- American Association of Poison Control Centers National Poison Data System (NPDS)
- National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project
- Premarket development programs
- Safety data bases from other FDA Centers

Principles:

Use Multiple Data Sources (cont'd)

Additional data sources (cont'd)

- Product utilization data
- Epidemiological studies
- Sentinel analyses
- Computational tools and predictive modeling
- Communication with international regulators
- Advisory committee meetings or other external input

Principles of Postmarket Safety Surveillance

- Multi-disciplinary, life-cycle approach
- Use multiple/all available data sources
- Risk-based approach

Risk-based Approach: Products for Monitoring

- New Drug Application products that are new molecular entities
- Original Biologic License application and biosimilar biological products
- First in class approved products
- Products with newly approved formulation
- Products with newly approved indication
- Extension into new patient populations (e.g., pregnant, pediatric, geriatric)
- Products with complex pharmacokinetic or pharmacodynamic characteristics
- Products with complex compositions or manufacturing processes

Risk-based Approach: Safety Information of Interest

- Important potential risks of the product recognized at the time of or after approval
- Apparent increase in the severity or frequency of reporting of a labeled adverse event (AE)
- Deaths, particularly in populations or in patients using the product for indications for which there would not be the expectation of death
- AEs for which causal attribution to the product is biologically plausible, based on the product's known pharmacological action
- Reports of unlabeled, serious AEs
- Serious AEs thought to be rare in the general population and associated with a high product-attributable risk

Risk-based Approach: Safety Information of Interest (cont'd)

- Interactions among different products (e.g., drug-drug, drug-device, drug-food, or drug-dietary supplement)
- Reports of reduced effectiveness or efficacy
- Medication errors resulting from confusion about a product's name, labeling, packaging, or use
- Off-label use, misuse, abuse, and other intentional uses of a product in a manner that is inconsistent with the FDA-approved labeling
- AEs reported or observed in a specific patient population
- AEs that for which a Risk Evaluation and Mitigation Strategy (REMS) is intended to mitigate the risk

Phases of Postmarket Safety Surveillance



- Identify safety signals
- Triage and prioritize safety signals
- Evaluate safety signals
- Take regulatory actions
- Communicate safety information

Weekly Screening

FAERS

- Focus on newly-received reports
- Risk-based approach in selecting products and AEs (slides 14, 15, and 16 on risk-based approach)
- Build customized alerts
- Data mine FAERS
- Follow up with the reporter

Medical literature

- Identify emerging safety signals that are not submitted as individual case safety reports (ICSR) to FDA
- Set up alerts in Embase and PubMed for select products and safety issues (slides 14, 15, and 16 on risk-based approach)

Summary Analysis of Cumulative Data

- Generally conducted at 12-18 months after initial FDA approval
- Analyze cumulative postmarket safety data in FAERS, medical literature, and PSRs since product approval
- Provide an aggregate, high-level summary of the reported postmarketing safety experience

Pediatric-focused Safety Reviews

- Triggered 18 months after the date of a labeling change for the drug
 - Reflects studies conducted under Pediatric Research Equity Act (PREA) or Best Pharmaceuticals for Children Act (BPCA)
- Inform the Pediatric Advisory Committee and the general public about the safety profile of drug products for the pediatric population (birth to 17 years old)
- Multidisciplinary, collaborative process

Phases of Postmarket Safety Surveillance



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Phases of Postmarket Safety Surveillance



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Evaluation of Prioritized Safety Signal

- Assemble a multidisciplinary team
- Complete a detailed assessment of all appropriate data sources
 - Determine causal association between the safety signal and the product

Evaluation of Prioritized Safety Signal (cont'd)

Detailed assessment of all appropriate data sources

- Build an informative FAERS and literature case series
- Consider the strength of evidence from the totality of data (slides 10, 11, and 12), including:
 - Drug utilization evaluation
 - Epidemiological studies
 - Sentinel analyses

Phases of Postmarket Safety Surveillance



- Identify safety signals
 - Signal refinement
- Triage and prioritize safety signals
- Evaluate safety signals
- Take regulatory actions
- Communicate safety information

Regulatory Actions

- Recommend or require the applicant to change the product labeling
- Require a postmarketing study or trial
- Require a new REMS or modify an approved REMS

Communications

- MedWatch Safety Alert
- Drug Safety Communication
- Web posting of potential safety signals
- Dear Health Care Provider letter (by the applicant)
- Literature publication and scientific meeting

Challenge Question #1

Which of the following is not a principle of postmarket safety surveillance?

- A. Use multiple/all available data sources
- B. Multidisciplinary, life-cycle approach
- C. Risk-based approach
- D. Take regulatory actions**

Challenge Question #2

Which of the following is a type of communication strategy?

- A. MedWatch Safety Alert
- B. Drug Safety Communication
- C. Web posting of newly identified safety signals
- D. Dear Health Care Provider letter (by the applicant)
- E. All of the above



Backup Slides

FDA's Interpretation of Signal

- Information that arises from one or multiple sources (including observations and experiments), that suggests a new potential causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.*
- The term signal is used to describe adverse (and not beneficial) events in the context of safety surveillance.

* The guidance for industry *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

POLICY AND PROCEDURES

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Collaborative Identification, Evaluation, and Resolution of a
Newly Identified Safety Signal (NISS)

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CDER's Criteria for NISS

The information represents:

- A serious adverse event; medication error; or an adverse event that suggests therapeutic inequivalence or product quality issue; **AND** the information indicates a likely safety signal that warrants further investigation into whether there is a causal association or a new aspect of a known association.

-OR-

- A product quality issue that:
 - could negatively affect public health or the benefit–risk profile of a product; and
 - cannot be resolved through existing routine processes (e.g., drug recalls, adverse inspection findings).

Questions?

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