Introduction to Postmarketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER

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Outline

• FDA organizational structure
• Postmarketing surveillance and FDA Adverse Event Reporting System (FAERS)
• Signal detection
• Case series development and evaluation
• Signal strengthening
• Communicating safety findings
Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

## Premarket vs Postmarket Safety Data

<table>
<thead>
<tr>
<th>Limitations of Premarket Clinical Trials</th>
<th>Benefits of Postmarket Safety Reporting</th>
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<tr>
<td>• Relatively small size of patient population</td>
<td>• Low frequency/rare Adverse Events</td>
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<td>• Narrow population/indications</td>
<td>• Captures adverse events (AEs) from entire population/includes all indications</td>
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<td>• Short duration</td>
<td>• Drug-drug/food interactions</td>
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<td>• Detect ↑ severity of known reactions</td>
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<td>• Direct engagement of healthcare professionals/consumers</td>
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Postmarket Adverse Event Reporting and FDA Adverse Event Reporting System (FAERS)
FDA Adverse Event Reporting System

- Computerized database of spontaneous reports
  - Voluntary communication from an individual (e.g., healthcare professional, consumer)
  - Mandatory reporting requirements for manufacturers
- Contains human drug and therapeutic biologic reports
- As of September 30, 2018:
  - 16,470,915 million reports received since 1969
  - Over 1.8 million new reports received in 2017

Federal Register - Code of Federal Regulations. 21 CFR 314.80 (a)
Number of Adverse Event Reports Entered into FAERS

Data as of September 30, 2018
How Postmarketing Reports Get to FDA

Patients, consumer, and healthcare professionals

Voluntary

FDA MedWatch

~5% of all reports

Manufacturer

~95% of all reports

Voluntary

FDA

FAERS Database

Regulatory Requirements
Factors Affecting Reporting Trends

• Publicity
  – Media attention
  – Litigation (class action lawsuits)

• Length of time on market
  – Type of drug product

• New indications for an approved drug

• Modifications in a company’s reporting requirements

• Changes in reporting regulations
FAERS Strengths and Limitations

Strengths

• Includes all marketed products, uses, and patient populations
• Especially good for
  • Rare events
  • Events that occur shortly after exposure

Limitations

• Cannot estimate incidence (underreporting)
• Dependent on report quality
• Events that could be manifestations or worsening of the disease for which the drug is indicated
• Events with a long latency
Safety Signal Detection

Did you see it??
What is a Safety Signal?

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially 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.
Select Sources of Possible Safety Signals

1. FAERS
2. Empirica Signal

Sources of Possible Safety Signals

- Clinical trials
- Pharmaco-vigilance Databases
- Medical Literature
- Media
- Manufacturer Global Safety Database
- Outside Inquiry
- Foreign Regulatory Agencies
- Observational Studies
- Sentinel

Monitoring FAERS for Safety Signals

- Safety Evaluators are assigned a drug portfolio
- Weekly FAERS “inbox” for newly received reports
- Risk-based principles utilized for report screening
Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation; does not prove causation
- Supplements FAERS data review
- Does not replace expert clinical case review
Case Series Development and Evaluation
Developing a Case Series

1. Identify a safety signal
2. Complete FAERS/literature search
3. Formulate case definition based on clinical diagnosis of event
4. Apply case definition for case selection
5. Evaluate case for presence of drug-event association

Components of a Good Postmarketing Report

- Description of adverse event
- Suspected and concomitant product therapy details (e.g., dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

Causality Assessment

Key factors in causality assessment

- Temporal relationship
- Biologic plausibility
- Rule out alternative etiologies
- Consistency (e.g., class effect)
- Dechallenge/Rechallenge
- Dose-response relationship

Signal Strengthening through Collaboration

• Collaboration within our Office
  • Epidemiology, including Drug Use
    • Evaluate observational studies
    • Quantify a drug-event association
    • Calculate reporting rates
  • Risk Management
    • Develop Risk Evaluation and Mitigation Strategy
• Collaboration outside of our Office within FDA
  • FDA colleagues in other offices
  • Other agencies (e.g., CDC)
Regulatory Actions and Communication

1. Boxed Warning
2. Warnings & Precautions
3. Adverse Reactions

Post Marketing Requirement (PMR); Epidemiologic Studies by FDA (e.g., Sentinel)

Risk Evaluation and Mitigation Strategy (REMS)

Market Withdrawal

Methods of communication:
1. Drug Safety Communication
2. Publications and scientific meetings
3. Quarterly webposting of new safety information from FAERS (FDAAA 921)
Questions?
How to Report:

- Online (www.fda.gov/medwatch)
- Download the form
- Mail
- Fax 1–800–332–0178

For questions about the form:

1–800–332–1088
Consumer MedWatch Form

- MedWatch Form 3500B
- Includes 4 primary components
  - Patient
  - Product
  - Event
  - Reporter
- User-friendly format for non-health care professionals
Definition of Serious Outcomes

Outcomes of:

- Death
- Life-threatening adverse experience
- Inpatient hospitalization – new or prolonged
- Persistent/significant disability or incapacity
- Congenital birth defect
- Other serious: based upon appropriate medical judgment, these AEs may jeopardize the patient and require intervention to prevent a serious outcome

Federal Register - Code of Federal Regulations. 21 CFR 314.80 (a)
Postmarketing Safety Reporting Requirements

- Under 21 CFR 314.80 postmarketing safety reports must be submitted to FDA for the following:
  - **Expedited reports**: Both **serious** and **unexpected** adverse experience from all sources (domestic and foreign)
    - Expedited Reporting
  - **Non-expedited reports**: Domestic spontaneous adverse events that are:
    - Serious and expected
    - Non-serious and unexpected
    - Non-serious and expected
    - Quarterly for the first 3 years then annually (for New Molecular Entity)