Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER

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Center of Drug Evaluation and Research
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Objectives

- Define Pharmacovigilance
- Describe the Division of Pharmacovigilance’s (DPV’s) key safety roles in FDA’s Center for Drug Evaluation and Research (CDER).
- Understand components of postmarketing drug safety surveillance.
- Understand regulatory requirements and the role of MedWatch for reporting postmarketing safety information.
- Describe how adverse event reports are collected and analyzed by FDA/CDER/DPV
Outline

- Pharmacovigilance Background
- Postmarketing Surveillance
- Spontaneous Adverse Event Reports and the FDA Adverse Event Reporting System (FAERS)
- Signal Detection
- Components of a Good Case Report
- Case Series Development and Evaluation
Office of Surveillance & Epidemiology

Office of Surveillance & Epidemiology

Office of Pharmacovigilance & Epidemiology

Division of Pharmacovigilance I and II (DPV I and II)

Division of Epidemiology I and II (DEPI I and II)

Division of Medication Error Prevention & Risk Management

Division of Medication Error Prevention & Analysis (DMEPA)

Division of Risk Management (DRISK)
Pharmacovigilance

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

*The Importance of Pharmacovigilance, World Health Organization 2002*
Divisions of Pharmacovigilance

- Evaluate the safety of drug and therapeutic biologic products
- Advance public health by detecting and analyzing safety signals from all available data sources, utilizing evidence-based methods
- Recommend appropriate regulatory actions, including labeling changes, Risk Evaluation and Mitigation Strategies (REMS), etc.
- Communicate relevant safety information
Safety Evaluators (SEs)

• 10 teams of SEs
  – Majority clinical pharmacists
  – Provide critical analysis of sources of postmarketing data to identify and evaluate safety signals

• Team coverage aligned with the Office of New Drugs (OND) review divisions’ therapeutic areas
  – ~ 4-7 SEs per team (including Team Leader)
  – Each SE covers assigned product group(s) aligned with therapeutic area
Medical Officers (MOs)

• Provide clinical expertise in various therapeutic areas such as dermatology, oncology, rheumatology, etc.
• Collaborate with DPV teams on safety evaluation
• Collaborate with Office of New Drugs (OND) on safety evaluation
Postmarketing Surveillance
Challenge Question #1

True or False

Safety data is only collected during the later phases of the clinical development program for a medical product.
Safety in the Lifecycle of FDA-regulated Products

- **Pre-clinical**
  - Safety & Biological Activity

- **Phase 1**
  - Safety & Dosage

- **Phase 2**
  - Safety & Efficacy

- **Phase 3**
  - Safety & Efficacy

- **Post-Marketing**
  - Safety Surveillance

Safety Concerns

Strategies and Actions to Minimize Risk
Limitations of Premarketing Clinical Trials

- Size of the patient population studied
- Narrow population - often not providing sufficient data on special groups
- Narrow indications studied
- Short duration
Benefits of Postmarketing Monitoring

The ability to study the following:

- Low frequency reactions (not identified in clinical trials)
- High risk groups
- Long-term effects
- Drug-drug/food interactions
- Increased severity and/or reporting frequency of known reactions
Types of Postmarketing Surveillance

• Spontaneous/voluntary reporting of cases
  – National (FDA MedWatch)
  – Local or Regional (Joint Commission Requirement)
  – Scientific literature publications

• Postmarketing studies (voluntary or required)
  – Observational studies (including automated healthcare databases)
  – Randomized clinical trials

• Active surveillance
  – Drug-Induced Liver Injury Network (DILIN)
  – Sentinel initiative
Postmarket Adverse Event Reporting and MedWatch
Challenge Question #2

Which of the following countries does not require practitioners to report adverse events to a national registry?

A. France
B. Norway
C. Sweden
D. US
How Postmarketing Reports Get to FDA

Patients, consumer, and healthcare professionals

Voluntary

FDA MedWatch

Manufacturer

Voluntary

FDA

5% of all reports

95% of all reports

FAERS Database

Regulatory Requirements
Postmarketing safety reporting requirements

- Under 21 CFR 314.80 postmarketing safety reports must be submitted to the agency for the following:
  - **15-day Alert reports**: Serious and unexpected adverse experience from all sources (domestic and foreign)
  - **Periodic Adverse Events 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
Serious Adverse Event

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

*Federal Register - Code of Federal Regulations. 21 CFR 314.80 (a)*
Spontaneous Reports and FAERS
Challenge Question #3

True or False?

The incidence of adverse drug events can be determined through spontaneous reporting systems.
Spontaneous Reports

- A communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority
- Describes a suspected adverse event(s)
- Passive and voluntary reports
Factors Affecting Reporting

- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event
- Type of drug product and indication
- Length of time on market
- Extent and quality of manufacturer’s surveillance system
- Prescription or over-the-counter (OTC) product status
- Reporting regulations
FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 9 million reports since 1969
- Over 1.2 million new reports in 2014
Number of Adverse Event Reports Entered into FAERS
FAERS Strengths

- Includes all U.S. marketed products
- Includes all uses
- Includes broad patient populations:
  - elderly, children, pregnant women, co-morbidities
- Especially good for events with a rare background rate
- Useful for events that occur shortly after exposure
- Detection of events not seen in clinical trials ("signal generation")
- Identification of reporting trends, possible risk factors, at risk populations, and other clinically significant emerging safety concerns
FAERS is less useful for:

- Events with high background rates
- Worsening of pre-existing disease
- Issue is beyond the name of the drug
- Comparative incidence rates
- Comparing drugs in the same class
- Adverse events that could also be manifestations of the disease for which the drug is indicated
- Reporting biases
Safety Signal Detection
Challenge Question #4

A safety signal could be:

A. New, previously unknown, adverse event
B. New drug interaction
C. An observed change in quantity, severity or the affected populations of a known adverse event
D. All of the above
What is a Safety Signal?

- Reported information on a possible causal relationship between an adverse event and a drug
- The relationship being previously unknown or incompletely documented
- Usually supported by multiple case reports
- New unlabeled adverse events
- An observed increase in a labeled event OR a greater severity or specificity
- New interactions
- Newly identified at-risk population
Sources of Possible Safety Signals

- Routine pharmacovigilance
  - FAERS
  - Data mining
  - Periodic Safety Update Reports from drug manufacturers
- Study results
- Medical literature
- Media
- New Drug Application (NDA) safety database
- Outside inquiry
- Foreign Regulatory Agencies
- Others
Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation
- Supplements FAERS data review
- Does not replace expert clinical case review
How to report to MedWatch
### Reporting to MedWatch

#### Patient Identifier
- **Patient Identifier**

#### Event or Problem
- **Event or Problem**

#### Reporter
- **Reporter**

#### Product
- **Product**

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**MEDWATCH**

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

**Form Approved**

**FDA USE ONLY**

**Page 1**

<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Event or Problem</th>
<th>Reporter</th>
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<td>Patient Status:</td>
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<tr>
<td>Patient Unique ID:</td>
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**Product Information**

- **Product:**
- **Manufacturer:**
- **Operator of Device:**

**Other Concomitant Medical Products**

- **Other Concomitant Medical Products:**

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**Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.**
**Consumer MedWatch Form**

**MedWatch Form 3500B**
- Includes 4 primary components
  - Patient
  - Product
  - Event
  - Reporter
- User-friendly format for non-health care professionals
• 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
Components of a Good Case Report
Case #1

A health care worker reported a male patient started Drug X at 5 mg daily for type 2 diabetes on February 11, 2011. On an unknown date, the patient developed liver failure; additional information was not provided.
Case #2: Best Case Representative

- 59-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of liver disease.
- Started Drug X on February 11, 2011.
- Other medications: simvastatin and lisinopril.
- Labs drawn on Feb 11 revealed Liver enzymes, INR, creatinine, and bilirubin all within normal limits.
- No alcohol use.

- 8 weeks after starting Drug X patient presented to ER with 5 day history of jaundice, dark urine, and nausea/vomiting.
- He was admitted to ICU and subsequently diagnosed with acute liver failure.
- Drug X stopped upon admission.
- Viral hepatitis was ruled out.
- 7 days after stopping the medication, all lab values returned to normal.
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

Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005
Case Series Development and Evaluation
Developing a Case Series

- Identify a well-documented case in FAERS, published literature, data mining, or other sources to identify a safety signal.
- Using our knowledge of the clinical course of the disease, formulate a case definition which may include both clinical features and laboratory findings, sometimes even demographic information if we believe the safety signal is for a specific population.
- Complete a thorough database search for additional cases.
Principles of Case Evaluation

- Temporal relationship
- Causality assessment- World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified
- Key factors in causality assessment including, but not limited to
  - Dechallenge/rechallenge
  - Comorbidities
  - Concomitant medications
  - Consistent with pharmacological effects (biologic plausibility)
Regulatory Actions

- Market Withdrawal
- REMS
- PMR/PMC Enhanced Pharmacovigilance
- Adverse Reactions
- Dear HCP Letter or DSC
- Boxed Warning
- Warnings And Precautions
- Regulatory Action
Regulatory Actions

- Product information changes – Warnings, Precautions, Adverse Reactions
- Pharmacovigilance activities - enhanced surveillance (e.g., expedited reporting), registry, epidemiology studies
- Risk Evaluation and Mitigation Strategy (REMS)
  - Communication plan, restricted use
- Drug Safety Communication (DSC)
- Market withdrawal
Communicating Safety Issues
Communicating Safety Issues to the Public and Internationally

- MedWatch Safety Alerts
- Postmarket Drug and Biologic Safety Evaluations (FDAAA 915)
- Potential Signals of Serious Risks/New Safety Information Identified from FAERS (FDAAA 921)
- Published literature and scientific meetings
- Video and teleconferences with foreign regulatory agencies:
  - EMA: European Medicines Agency
  - 4-Way: Canada, Australia, New Zealand, (Singapore in writing)
MedWatch: The FDA Safety Information and Adverse Event Reporting Program

What's New

- Heart Sync Inc. Multi-function Defibrillation Electrodes: Device Correction - Connector Incompatibility with Philips FR3 and FRx Defibrillator Units May result in a delay in therapy. Posted 12/03/2014

- Gel-E Donut and Squishon 2 Products by Children's Medical Ventures: Recall - Potential Mold Contamination UPDATED 12/02/2014. Recall classified as Class I. Possibility of fungal infection should patients come in contact with mold. Originally posted 11/14/2014

FDA Approved Safety Information

- DailyMed (National Library of Medicine)
  Current Drug Prescribing Information. (NOTE: Drugs marked "unapproved" on this site have not been reviewed by FDA for safety and efficacy, and their labeling has not been approved.)

- Medication Guides
  Paper handouts that come with many prescription medicines. Medication Guides address issues specific to particular drugs and drug classes. They contain FDA-approved information that can help patients avoid serious adverse events.

- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)

- Postmarket Drug and Biologic Safety Evaluations
  Evaluations performed 18 months after drug approval, or after its use by 10,000 individuals.
http://www.fda.gov/Safety/MedWatch
Questions
References

Acronyms

- CDER – Center for Drugs Evaluation & Research
- CFR – Code of Federal Regulations
- DEPI I & II – Division of Epidemiology I & II
- DILIN – Drug-Induced Liver Injury Network
- DMEPA – Division of Medication Error & Prevention Analysis
- DPV I & II – Division of Pharmacovigilance I & II
- DRISK – Division of Risk Management
- DSC – Drug Safety Communication
- EMA – European Medicines Agency
- FDA – Food & Drug Administration
Acronyms, cont’d

• FDAAA – Food & Drug Administration Amendment Act
• FAERS – FDA Adverse Events Reporting System
• HCP – Health Care Provider
• MO – Medical Officer
• NDA – New Drug Application
• OND – Office of New Drugs
• PMC – Postmarketing Commitment
• PMR – Postmarketing Requirement
• REMS – Risk Evaluation & Mitigation Strategy
• SE – Safety Evaluator
• WHO-UMC – World Health Organization – Uppsala Monitoring Centre
FAERS Metrics

Reports per Year

Reports by Source Type per Year

Reports by Reporter Type per Year

Reports by Age Group and Gender per Year