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

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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
• Case Series Development and Evaluation
• Components of a Good Case Report
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 (DMEPA)

Division of Risk Management (DRISK)

Division of Medication Error Prevention & Risk Management (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)

• Currently 11 MOs
• Provide clinical expertise in various therapeutic areas such as dermatology, infectious disease, rheumatology, pediatrics, 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

APPROVAL

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

Regulatory Requirements

FDRA Voluntary

Voluntary

5% of all reports

95% of all reports

FDA

FAERS Database

5% of all reports

95% of all reports
Reporting In To MedWatch

1. Patient Identifier
2. Product
3. Event or Problem
4. Reporter

Form for reporting adverse events, product problems or errors.

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

[Image of MedWatch form]

Patient Identifier: [Input field]

Product: [Input field]

Event or Problem: [Input field]

Reporter: [Input field]
• 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
Spontaneous Reports and FAERS
Challenge Question #3

True or False

The actual incidence of adverse drug reactions can never 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
- Rx or OTC product status
- Reporting regulations
FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 7 million reports since 1969
- Nearly 1 million new reports in 2012
Number of Adverse Event Reports Entered into FAERS

Growing Number of Adverse Event Reports

- PERIODIC (Non-Expedited)
- 15-DAY (Expedited)
- DIRECT

Calendar Year

Number of Reports
**FAERS Strengths**

- Includes all U.S. marketed products
- Includes all uses
- Includes broad patient populations:
  - elderly, children, pregnant women, co-morbidities
- Simple, relatively inexpensive reporting system
- 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 trends, possible risk factors, populations, and other clinically significant emerging safety concerns
Limitations of FAERS

- 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
- Disease is reflected in the adverse event
- Looking for drug interactions
- Reporting Biases
Safety Signal Detection

Did you see it??
Challenge Question #4

A safety signal is defined as:

A. New, previously unknown, adverse event
B. New drug interaction
C. An observed increase, either in quantity or severity, 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 requires more than a single case report to generate a signal

- 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
  - Datamining
  - Periodic Safety Update Reports
- 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 or support for further work on a hypothesis
- Supplements FAERS data review
- Does not replace expert clinical case review
Case Series Development and Evaluation
Developing a Case Series

- Use FAERS, published literature, Datamining and other sources to identify safety signal.
- Use knowledge of the clinical course of the disease to perform a thorough database search strategy based on Medical Dictionary for Regulatory Activities (MedDRA) coding
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

- Labeling changes – i.e. 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
- Market withdrawal
- Drug Safety Communication (DSC)
Communicating Safety Issues
Communicating Safety Issues to the Public and Internationally

- MedWatch Safety Alerts
- Drug Safety Newsletter
- 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 tele-conferences with foreign regulatory agencies:
  - European Medicines Agency, Canada, Australia, New Zealand
MedWatch: The FDA Safety Information and Adverse Event Reporting Program

Your FDA gateway for clinically important safety information and reporting serious problems with human medical products.

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Resources for You
- Report a Serious Medical Product Problem Online
- Reporting Unlawful Sales of Medical Products on the Internet
- Current Drug Shortages Index
- Index to Drug Specific Information
- Identifying Recalled Products
- An FDA Guide to Drug Safety Terms

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What's New
- Samsca (tolvaptan): Drug Warning - Potential Risk of Liver Injury
  *Large clinical trial findings of significant elevations of both ALT and bilirubin. Posted 01/25/2013*
- Bausch and Lomb 27G Sterile Cannula Packed in Amvisc Plus Ophthalmic Viscosurgical Devices (OVD): Class I Recall - Cannulas May Leak or Detach From the Syringe
  *Some disposable cannulas provided may leak viscoelastic material or detach from the syringe during injection. In rare incidences, detachment has resulted in serious patient injury. Posted 01/23/2013*
- Ferrous Sulfate Tablets, 325 mg Labelled as Rugby Natural Iron Supplement: Recall - Bottle May Contain Medication HCl 25 mg
  *Serious adverse events may include impaired alertness, drowsiness, confusion, low blood pressure, coma, and respiratory depression. Posted 01/18/2013*

More What's New

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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) (formerly AERS)*
- Postmarket Drug and Biologic Safety Evaluations
  *Evaluations performed 18 months after drug approval, or after its use by 10,000 individuals.*

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Spotlight
- 2013 Safety Alerts for Human Medical Products
- Bad Reactions to Cosmetics? Tell FDA! 
- Medical Product Safety Educational Resources
- MedWatch Partners

Recalls & Alerts
- MedWatch Safety Alerts for Human Medical Products
- FDA Patient Safety News Video Broadcasts
- FDA Drug Safety Newsletter

Stay Informed
- Subscribe to MedWatch Safety Alerts
- Join the MedWatch E-list
- About the MedWatch E-list
- Follow MedWatch on Twitter
- MedWatch Safety Alerts RSS Feed
- RSS News Feed Help
http://www.fda.gov/Safety/MedWatch
Components of a Good Case Report
Case #1

A nurse 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 yr/ male with history of type 2 diabetes, hyperlipidemia, and hypertension. Patient had no history of liver disease
- Started Drug X on February 11, 2011.
- Other medications include simvastatin and lisinopril.
- Labs drawn on Feb 11 revealed Liver enzymes, INR, Creatinine, and bilirubin normal
- Patient does not drink alcohol
- 8 weeks after starting Drug X patient presented to ER with 5 day history of jaundice, dark urine, and nausea/vomiting
- Admitted to ICU and diagnosed with acute liver failure.
- Drug X stopped upon admission
- All viral hepatitis was ruled out.
- 7 days after stopping 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
Questions
References

• MedWatch: The FDA Safety Information and Adverse Event Reporting Program: http://www.fda.gov/Safety/MedWatch/default.htm
• MedWatch Safety Alert RSS Feed: http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/MedWatch/rss.xml
• Postmarketing Drug and Biologic Safety Evaluations: (FDAAA 915): http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm
• Potential Signals of Serious Risks/New Safety Information Identified from AERS (FDAAA 921): http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm#QuarterlyReports