FDA’s Postmarketing Drug Safety Surveillance System

Kim Swank, PharmD
Division of Pharmacovigilance
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Objectives

- Describe FDA’s postmarketing drug safety surveillance system
- Identify the components of postmarketing reporting and signal detection
- Summarize how adverse event reports are collected and analyzed by FDA
- Describe how safety findings are communicated to the public
Outline

• FDA organizational structure
• Division of Pharmacovigilance
• Postmarketing surveillance and FDA Adverse Event Reporting System (FAERS)
• Components of a good case report
• Signal detection
• Case series development and evaluation
• 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.

Who Are We: Safety Evaluators and Medical Officers

• Group of mostly pharmacists and physicians
  – Provide clinical expertise in various therapeutic areas such as dermatology, oncology, neurology, etc.
  – Review the weekly FAERS “inbox” for newly received individual case safety reports
What do we do

• Advance public health by detecting safety signals from all available data sources
• Evaluate the safety of drugs
• Identification of reporting trends, possible risk factors, at risk populations, etc.
• Collaborate with other divisions (i.e., DEPI, DMEPA, DRISK)
• Recommend regulatory actions
• Communicate relevant safety information
Why does DPV exist?

• Among 222 novel therapeutics approved by FDA from 2001-2010, 32% were affected by a postmarket safety event:
  – New boxed warning
  – Withdrawal due to safety issue
  – FDA safety communication

• Variables associated with higher rates of events:
  – Biologics
  – Psychiatric therapeutics
  – Accelerated approval
  – Near-regulatory deadline approval
Postmarketing Safety Surveillance
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 Premarket Clinical Trials

- Relatively small size of patient population
- Narrow population/indications
- Short duration
- Lack of adequate ascertainment and classification of adverse events

### Benefits of Postmarket Safety Reporting

- Low frequency/rare Adverse Events
- Captures adverse events (AEs) from entire population/includes all indications
- Drug-drug/food interactions
- Detect ↑ severity of known reactions
- Direct engagement of healthcare professionals/consumers

Select Postmarketing Data Sources

- Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Scientific literature publications
- Postmarketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials
- Other surveillance tools
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel
  - National Electronic Injury Surveillance System -- Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)
  - National Poison Data System (NPDS)

Postmarket Adverse Event Reporting and FDA Adverse Event Reporting System (FAERS)
How Postmarketing Reports Get to FDA

- Patients, consumer, and healthcare professionals
  - Voluntary
  - FDA MedWatch
    - ~5% of all reports
  - Manufacturer
    - Regulatory Requirements
    - ~95% of all reports

FDA MedWatch

FAERS Database

~5% of all reports

Manufacturer

~95% of all reports
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)

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*Federal Register - Code of Federal Regulations. 21 CFR 314.80 (a)*
Serious Adverse Event

• Results in any of these outcomes:
  • 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
Factors Affecting Reporting

• Media attention
• Litigation (class action lawsuits)
• Nature of the adverse event
• Type of drug product and new indications
• Length of time on market
• Extent and quality of manufacturer’s surveillance system
• Reporting regulations

FDA Adverse Event Reporting System

• Computerized database of spontaneous reports
  – Voluntary communication from an individual (e.g., healthcare professional, consumer) describing one or more suspected AEs
• Contains human drug and therapeutic biologic reports
• As of December 31, 2019:
  • 19,181,605 million reports received since 1969
  • Over 2.18 million new reports received in 2019
Number of Adverse Event Reports Entered into FAERS

Reports Received by Report Type

Data as of December 31, 2019
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**
- Worsening of pre-existing disease
- Dependent on report quality
- Cannot estimate incidence (underreporting)
- Adverse events that could also be manifestations of the disease for which the drug is indicated

FAERS Public Dashboard

- Interactive web-based tool for querying FAERS data
- Freedom of Information (FOI) request to FDA
  - Individual case safety reports from FAERS database
  - Redacted case reports for privacy
- This public database does not have case narratives

https://www.fda.gov/about-fda/fda-pharmacy-student-experiential-program/division-drug-information-webinars
How to report to MedWatch
• 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**

![MedWatch Form 3500B](https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf)

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Reporting AEs for Biological Products

• Pharmacovigilance of biological products present a unique challenge due to naming convention

• Example
  • Non-proprietary (active ingredient or active substance): Filgrastim
    • Trade/brand name of originator product: Neupogen
  • Biosimilar #1: Filgrastim-sndz
    • Trade/brand name of U.S. biosimilar is Zarxio
  • Biosimilar #2: Filgrastim-aafi
    • Trade/brand name of U.S. biosimilar is Nivestym

Reporting AEs for Biological Products

• The optimal pharmacovigilance practice is to describe the suspect product using the nonproprietary name (i.e., combination of the core name and a distinguishing suffix)

• FDA Guidance for Industry changed in 2017 to recommend that all newly approved biological products (including both the originator and biosimilar) contain a meaningless 4-letter suffix
Reporting AEs For Brand vs Generic Products

• Manufacturers of brand name (innovator product) and generic products have identical regulatory obligations to report AEs

• Innovator manufacturers generally submit the vast majority of AE reports even after generic approval
  – This indicates patient and provider familiarity with brand names leading to preferential reporting to innovator manufacturers
Reporting AEs For Brand vs Generic Products

Clin Pharmacol Ther. 2015 May;97(5):508-17
Components of a Good Case Report
Case #1

A health care worker reported a male patient started Drug X at 500 mg daily for cellulitis on April 5, 2018. On an unknown date, the patient developed acute renal failure; additional information was not provided.
Case #2: Best Case Representative

- 60-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of renal failure.
- Started Drug X at 500 mg daily on April 5, 2018 for left leg cellulitis.
- Other medications: regular insulin, glyburide, atorvastatin, and lisinopril
- Labs drawn on April 5th revealed creatinine and BUN were within normal limits. Urinalysis was negative
- 4 days after starting Drug X patient presented to the ER with decreased urine output, edema, fever, and nausea
- Labs on admission: Scr 2.1 mg/dL, BUN 30 mg/dL
- Urinalysis: proteinuria, eosinophils, and renal tubular epithelial cells
- He was admitted to ICU and subsequently diagnosed with acute renal failure
- Drug X stopped upon admission
- 5 days after stopping the medication, all lab values returned to baseline
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
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

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

1. FAERS
2. Empirica Signal

Case Series Development and Evaluation
Developing a Case Series

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

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

• Collaborate with our OSE colleagues
  • Epidemiology, including Drug Use
    • Provide epidemiologic assessment, calculate reporting rates
    • Identify population at risk, risk factors, and quantify a drug-event association
  • Risk Management
    • Facilitate Risk Evaluation and Mitigation Strategy development
  • Medication Errors
• Collaborate with FDA colleagues, other Agencies (e.g., CDC)
Select sponsor and FDA actions

DSC = drug safety communication
REMS = risk evaluation and mitigation strategy
PMR/PMC = postmarketing requirement, postmarketing commitment

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Communication

Within FDA

• Maintain formal and informal communication and collaborative efforts with OND
  • Regular Safety Meetings with OND
• Regulatory Briefings

With FDA Stakeholders

• Drug Safety Oversight Board (DSB)
  • Representatives from AHRQ, CDC, CMS, DOD, FDA, HRSA, IHS, NIH, VA
• Teleconferences with foreign regulatory agencies:
  • European Medicines Agency (EMA)
  • International Post-Market Surveillance (IPMS): Canada, Australia, New Zealand, Switzerland, Singapore (via written submission)

Communicating Safety Issues to the Public and Scientific Community

• MedWatch Safety Alerts
  • Drug Safety Communication
• Potential Signals of Serious Risks/New Safety Information Identified from FAERS (FDAAA 921)
• Published literature and scientific meetings
• Advisory Committees
  • 49 committees of experts who can provide advice to FDA
Recent Safety Issues Investigated by DPV
Recent Drug Safety Communications

• Serious liver injury with the primary biliary cholangitis drug Ocaliva (obeticholic acid) (September 2017)
  • Boxed warning to highlight correct dosing for patients (February 2018)
• FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines (eszopiclone, zaleplon, zolpidem) (April 2019)
• Serious breathing problems with seizure and nerve pain medicines gabapentin and pregabalin (December 2019)

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease (2017). Available at: https://www.fda.gov/drugs/drugsafety/ucm576656.htm
Safety signal examples
Loperamide and cardiac AEs

- DSC describing serious cardiac AEs, including QT interval prolongation, Torsades de Pointes, and ventricular arrhythmias were reported to FAERS.
- Cases were mostly in individuals taking high doses of loperamide in situations of misuse/abuse.
Two publications were authored by the DPV reviewers to further inform the public of what has been reported to FAERS regarding cardiac adverse events with loperamide abuse.
Example of a Safety Signal Investigation - Ticagrelor
Ticagrelor – signal generation

- Case report of life-threatening complete atrioventricular (AV) block associated with ticagrelor therapy
  - Included FAERS cases that described AV block within one month of starting therapy and positive dechallenge or continued on therapy with a pacemaker
    - 26 cases found in FAERS
    - One case found in medical literature
    - 15 patients had AV block < 24 hours after the first dose of Ticagrelor
  - Warnings and Precautions added to the label
Ticagrelor Background

• Ticagrelor prevents platelet activation

• Indications:
  • Reduce the rate of cardiovascular death, myocardial infarction (MI) and stroke in patients with acute coronary syndrome (ACS) or a history of MI
  • Reduce the rate of stent thrombosis in patients who have been stented for treatment of ACS

• Dosage and Administration:
  • 180 mg loading dose then 90 mg twice daily for the first year then 60 mg twice daily thereafter

• Risk of bradycardia identified during a substudy

Example: Ticagrelor and atrioventricular block

- Inclusion criteria: AV block within one month of starting therapy and positive dechallenge or continued on therapy with a pacemaker
- 26 cases found in FAERS
- One case found in medical literature
- 15 patients had AV block < 24 hours after the first dose of ticagrelor

Ticagrelor Labeling

• WARNINGS AND PRECAUTIONS

5.5 Bradyarrhythmias

Ticagrelor can cause ventricular pauses [see Adverse Reactions (6.1)]. Bradyarrhythmias including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from PLATO and PEGASUS and may be at increased risk of developing bradyarrhythmias with ticagrelor.
2012 Fungal Meningitis Outbreak

- New England Compounding Center (NECC) fungal meningitis outbreak in 2012
  - Final case count: 753
  - Deaths: 64
  - States: 20
  - Cause: contaminated methylprednisolone injections
- NECC violated their state license by functioning as a drug manufacturer
- This tragedy highlighted the need for greater FDA authority in regulating compounded products

Centers for Disease Control and Prevention. Multistate Outbreak of Fungal Meningitis and Other Infections. Available at: https://www.cdc.gov/hai/outbreaks/meningitis.html
Patient received Drug X at the infusion clinic. The patient later called the clinic to say he developed meningitis and was hospitalized. Patient's wife called on 11/7/12 to let us know patient died.

Drug X

A. Pharmacist, A. University Hospital
### A. PATIENT IDENTIFIER

| JG | 69 yo | 189 lb |

### B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

- Date of Event: 10/15/12
- Diagnosis or Reason for Use (Indication): Back pain
- Date of Dose Use: 10/15/12

### C. SUSPECT MEDICAL DEVICE

- Drug X 125mg, XX Pharmacy
- Drug X was compounded by XX pharmacy. Drug X was received by our pharmacy on 10/13/12, lot number 23557, expiration date 10/19/12. Con't on pg 2...

### F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

**Drug X 125mg, XX Pharmacy**

### G. REPORTER

- Dr. Heath Filie
  - Clinical Pharmacist, Pain Clinic
  - Pennsylvania
  - (717) 555-8999
  - pills4U@yahoo.com

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Patient received his first dose of Drug X as an epidural infusion at the infusion clinic on 10/15/12 for back pain. The patient developed headache, fever, chills, and aches 2 days after the infusion. The patient was admitted to the hospital on 10/18/12 and diagnosed with meningitis. CSF cultures and blood cultures grew out Exserohilium rostratum. The patient was treated with voriconazole; however, the patient was immunocompromised and continued to decline. The patient died on 11/7/12.
Who regulates compounded drugs?

- State boards of pharmacy oversee state-licensed pharmacies that compound under 503A (compounding for specific patient prescription)
- NEW: Drug Quality and Security Act (DQSA) - 2013
  - Firms that register with FDA as outsourcing facilities under 503B are regulated by the FDA, inspected, and subject to cGMP requirements
  - Firms that do not register under 503B and do not meet 503A requirements are subject to new drug approval requirements

U.S. Food and Drug Administration. Compounding and the FDA: Questions and Answers. Available at: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm339764.htm#risks
Summary

• Pharmacovigilance
• Postmarketing surveillance
• FAERS
• How you can report adverse events
• How we use postmarketing reports to identify safety information
• What information is useful for our analysis
• How we communicate our findings
• Examples of safety signals
Questions?