FDA Drug Topics: An Overview of Pharmacovigilance in the Center for Drug Evaluation and Research (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).
• Explain components of postmarketing drug safety surveillance.
• Understand the role of MedWatch for reporting postmarketing safety information.
• Discuss how adverse event reports are collected and analyzed by FDA/CDER/DPV
Outline

• FDA organizational structure
• Division of Pharmacovigilance
• Postmarketing surveillance and FDA Adverse Event Reporting System (FAERS)
• How to report an adverse event
• Components of a good case report
• Signal detection
• Case series development and evaluation
• Communicating safety findings
Office of the Commissioner

Office of Foods and Veterinary Medicine
- Center for Food Safety & Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)

Office of Medical Products and Tobacco
- Center for Devices & Radiological Health (CDRH)
- Center for Biologics Evaluation & Research (CBER)
- Center for Drug Evaluation & Research (CDER)

Office of Global Regulatory Operations and Policy
- Center for Tobacco Products (CTP)

Office of Operations
- Center for Veterinary Medicine (CVM)

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Center for Devices & Radiological Health (CDRH)
Center for Food Safety & Applied Nutrition (CFSAN)
CDER

- Office of Translational Sciences
- Office of New Drugs
- Office of Generic Drugs
- Office of Pharmaceutical Quality
- Office of Surveillance and Epidemiology
- Office of Compliance

CDER

Office of New Drugs

Office of Generic Drugs

Office of Pharmaceutical Quality

Office of Surveillance and Epidemiology

Office of Compliance
Office of Surveillance & Epidemiology
Gerald Dal Pan, Director

Office of Pharmacovigilance & Epidemiology

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

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

Office 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.

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

- **Post-Marketing**
  - Approval
  - Safety Surveillance

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Safety Concerns

**Strategies and Actions to Minimize Risk**
## Premarket vs Postmarket Safety Data

### 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 \( \uparrow \) severity of known reactions
- Direct engagement of healthcare professionals/consumers

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Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm
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

~95% of all reports

FDA

Regulatory Requirements

FAERS Database
Postmarketing Safety Reporting Requirements

• Under 21 CFR 314.80 postmarketing safety reports must be submitted to FDA for the following:
  
  o **Expedited reports**: Both **serious** and **unexpected** adverse events from all sources (domestic and foreign)
    o Expedited Reporting
  
  o **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)

*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)
  - 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 December 31, 2018
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; however, limitations exist:
  ▪ Existence of a report does not establish causation
  ▪ This public database does not have case narratives
  ▪ Duplicate and incomplete reports
  ▪ Information in reports has not been verified
  ▪ Incidence cannot be established

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

Components of a Good Case Report
Case #1

A health care worker reported a female patient started Drug X at 25 mg daily for hypertension on September 14, 2015. On an unknown date, the patient developed Stevens-Johnson syndrome (SJS); additional information was not provided.
Case #2: Best Case Representative

- 62-year-old female with hypertension and depression
- No known allergies
- Started Drug X on September 14, 2015
- Other medications: citalopram and multi-vitamins
- Labs drawn on Sept 14 were all WNL
- BP was 145/85 mmHg
- 2 weeks after starting Drug X patient presented to ER with 2 day history of generalized rash on hands, face, and feet, weakness, arthralgia, and fever.
- On exam, she was noted to have conjunctival hyperemia, multiple-erythema-like eruptions with blisters on the skin that covered 10% or more of the body surface area.
- She was admitted to the hospital and subsequently diagnosed by a dermatologist with SJS.
- Drug X stopped upon admission and patient was treated with prednisone.
- Several days after stopping the medication, the eruptions resolved.
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??

signal
What is a Safety Signal?

• Reported information on a possible causal relationship between an adverse event and a drug
• The relationship is 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

Select Sources of Possible Safety Signals

1. FAERS
2. Data Mining

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

Disproportionality in FAERS

• Important tool in modern pharmacovigilance
• Helps drug safety scientists recognize patterns in large datasets
• Hypothesis generating activity, that does not prove causation
• Several test statistics are currently used
  – Proportional reporting ratio (PRR)
  – Reporting odds ratio (ROR)
  – Empirical Bayes Geometric Mean (EBGM)
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

Causality Assessment

Key factors in causality assessment

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

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

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)
• 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 obeticholic acid (September 2017)
  - Boxed warning to highlight correct dosing for patients (February 2018)
- Increased risk of serious pancreatitis with irritable bowel drug eluxadoline in patients without a gallbladder (March 2017)
- Rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate (February 2017)
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
Loperamide and cardiac AEs

- Since original DSC, warnings have been added to the drug labels for prescription and OTC loperamide products
- OTC package product counts were also restricted

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the anti-diarrheal medicine loperamide (Imodium), including from abuse and misuse (2016). Available at:https://www.fda.gov/drugs/drugsafety/ucm504617.htm
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.
2012 Fungal Meningitis Outbreak

• New England Compounding Center (NECC) fungal meningitis outbreak in 2012
  • Final case count: 753
  • Deaths: 64
  • States: 20
  • Cause: contaminated PF 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.
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.

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...

Please see accompanying file
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
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?