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

FDA

Office of the Commissioner

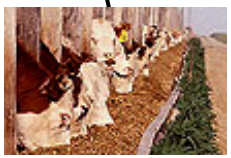
Office of Operations

Office of Foods and Veterinary Medicine

Office of Medical Products and Tobacco

Office of Global Regulatory Operations and Policy

Center for **F**ood **S**afety & **A**pplied **N**utrition **(CFSAN)**



Center for **V**eterinary **M**edicine **(CVM)**

Center for **D**evices & **R**adiological **H**ealth **(CDRH)**

Center for **B**iologics **E**valuation & **R**esearch **(CBER)**

Center for **D**rug **E**valuation & **R**esearch **(CDER)**

Center for **T**obacco **P**roducts **(CTP)**

Office of **R**egulatory **A**ffairs **(ORA)**

CDER

Office of Translational Sciences

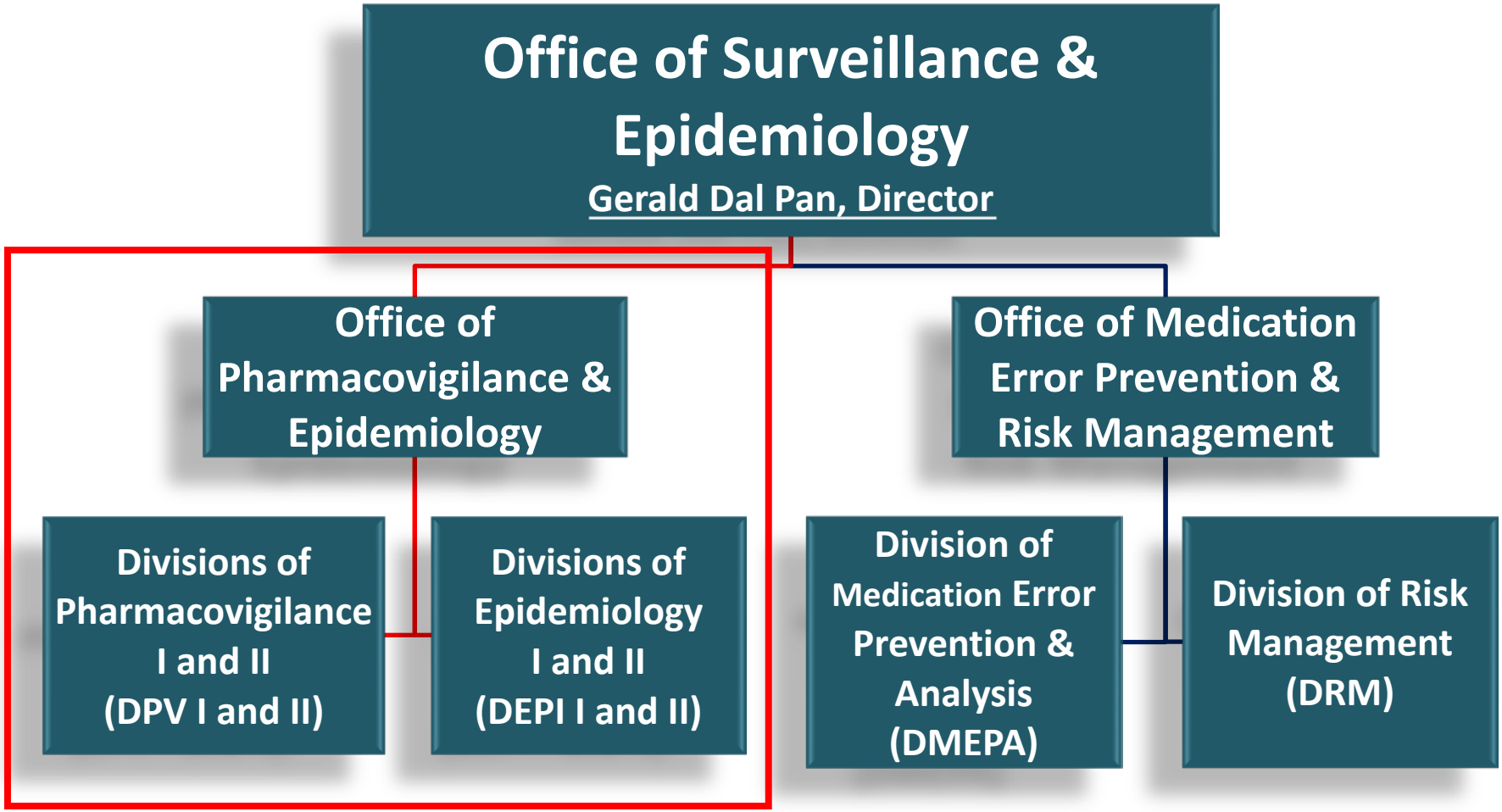
Office of New Drugs

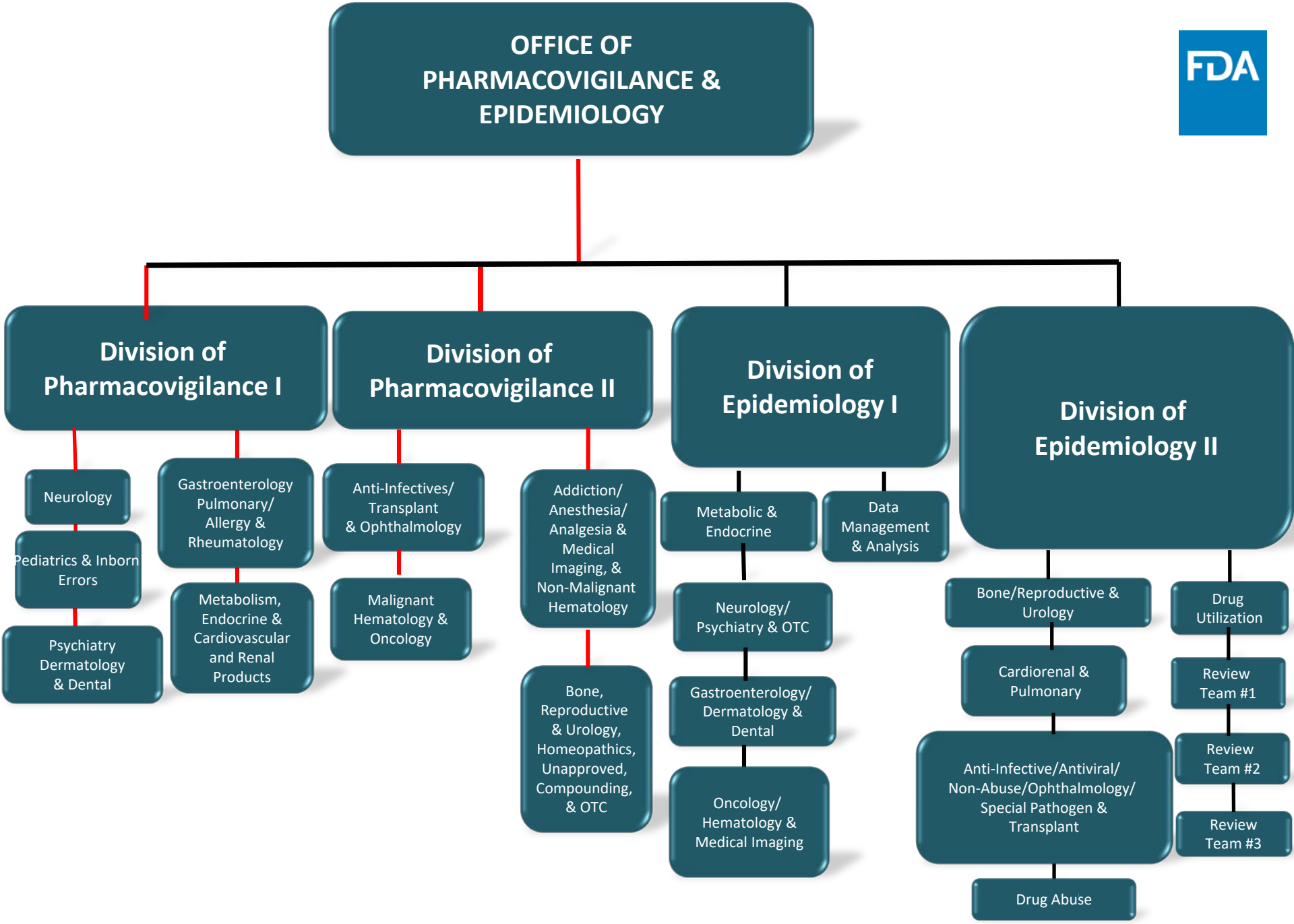
Office of Generic Drugs

Office of Pharmaceutical Quality

Office of Surveillance and Epidemiology

Office of Compliance


Office of Surveillance & Epidemiology
Gerald Dal Pan, Director
Office of Pharmacovigilance & Epidemiology
Office of Medication Error Prevention & Risk Management
Divisions of Pharmacovigilance I and II (DPV I and II)
Divisions of Epidemiology I and II (DEPI I and II)
Division of Medication Error Prevention & Analysis (DMEPA)
Division of Risk Management (DRM)


OFFICE OF PHARMACOVIGILANCE & EPIDEMIOLOGY
FDA
Division of Pharmacovigilance I
Neurology
Pediatrics & Inborn Errors
Psychiatry Dermatology & Dental
Gastroenterology Pulmonary/ Allergy & Rheumatology
Metabolism, Endocrine & Cardiovascular and Renal Products
Division of Pharmacovigilance II
Anti-Infectives/ Transplant & Ophthalmology
Malignant Hematology & Oncology
Addiction/ Anesthesia/ Analgesia & Medical Imaging, & Non-Malignant Hematology
Bone, Reproductive & Urology, Homeopathics, Unapproved, Compounding, & OTC
Division of Epidemiology I
Metabolic & Endocrine
Data Management & Analysis
Neurology/ Psychiatry & OTC
Gastroenterology/ Dermatology & Dental
Oncology/ Hematology & Medical Imaging
Division of Epidemiology II
Bone/Reproductive & Urology
Cardiorenal & Pulmonary
Anti-Infective/Antiviral/ Non-Abuse/Ophthalmology/ Special Pathogen & Transplant
Drug Abuse
Drug Utilization
Review Team #1
Review Team #2
Review Team #3

Pharmacovigilance

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

World Health Organization. The Importance of Pharmacovigilance: Safety Monitoring of medicinal products. (2002). Available at: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf?ua=1. Accessed March 8, 2018.

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?

JAMA | Original Investigation

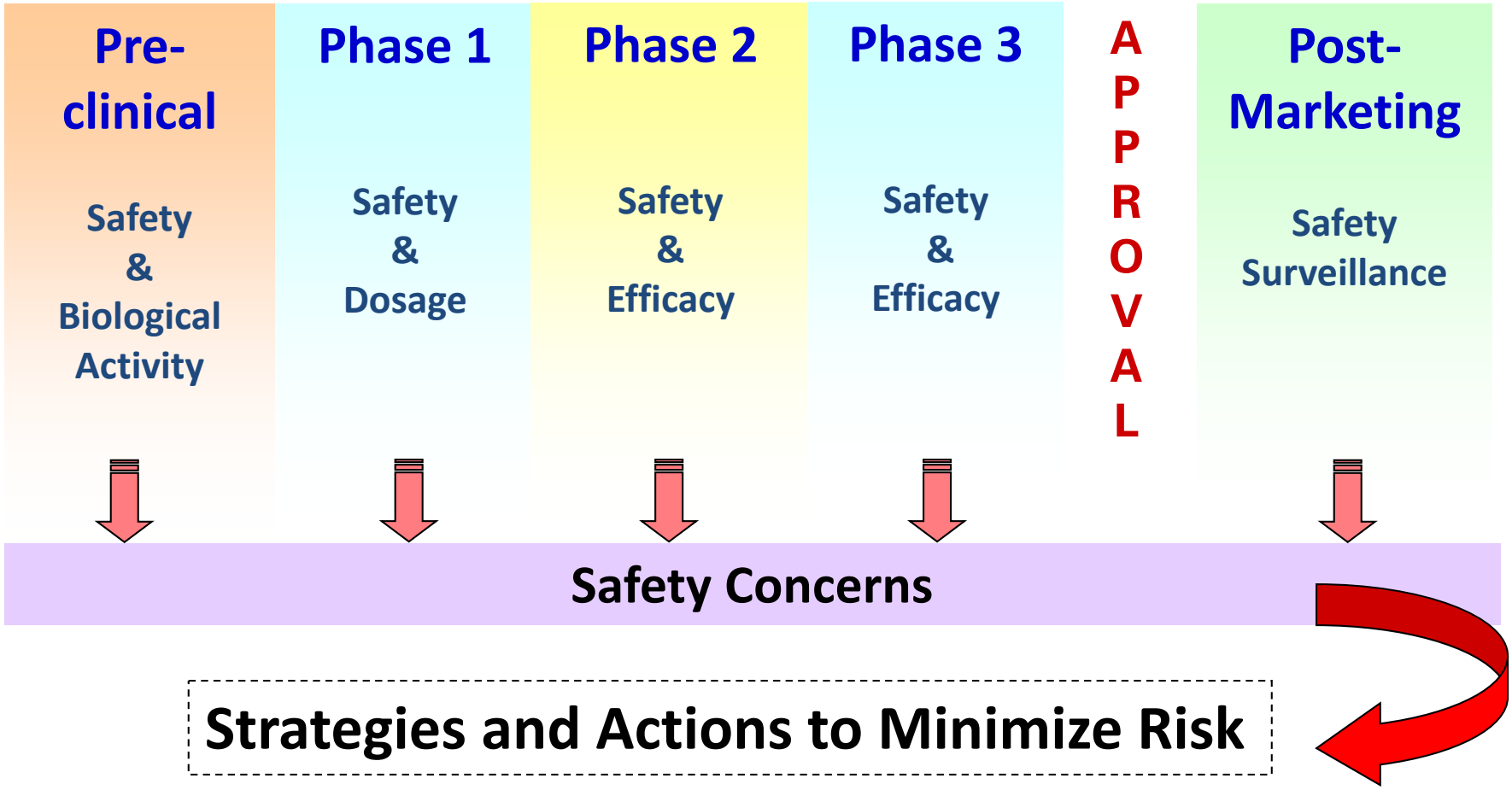
Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

- 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



Premarket vs Postmarket Safety Data

Limitations of Premarket Clinical Trials	Benefits of Postmarket Safety Reporting
• Relatively small size of patient population • Narrow population/ indications • Short duration • Lack of adequate ascertainment and classification of adverse events	• 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

Singh S et al. Trials. 2012;13:138
Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell.

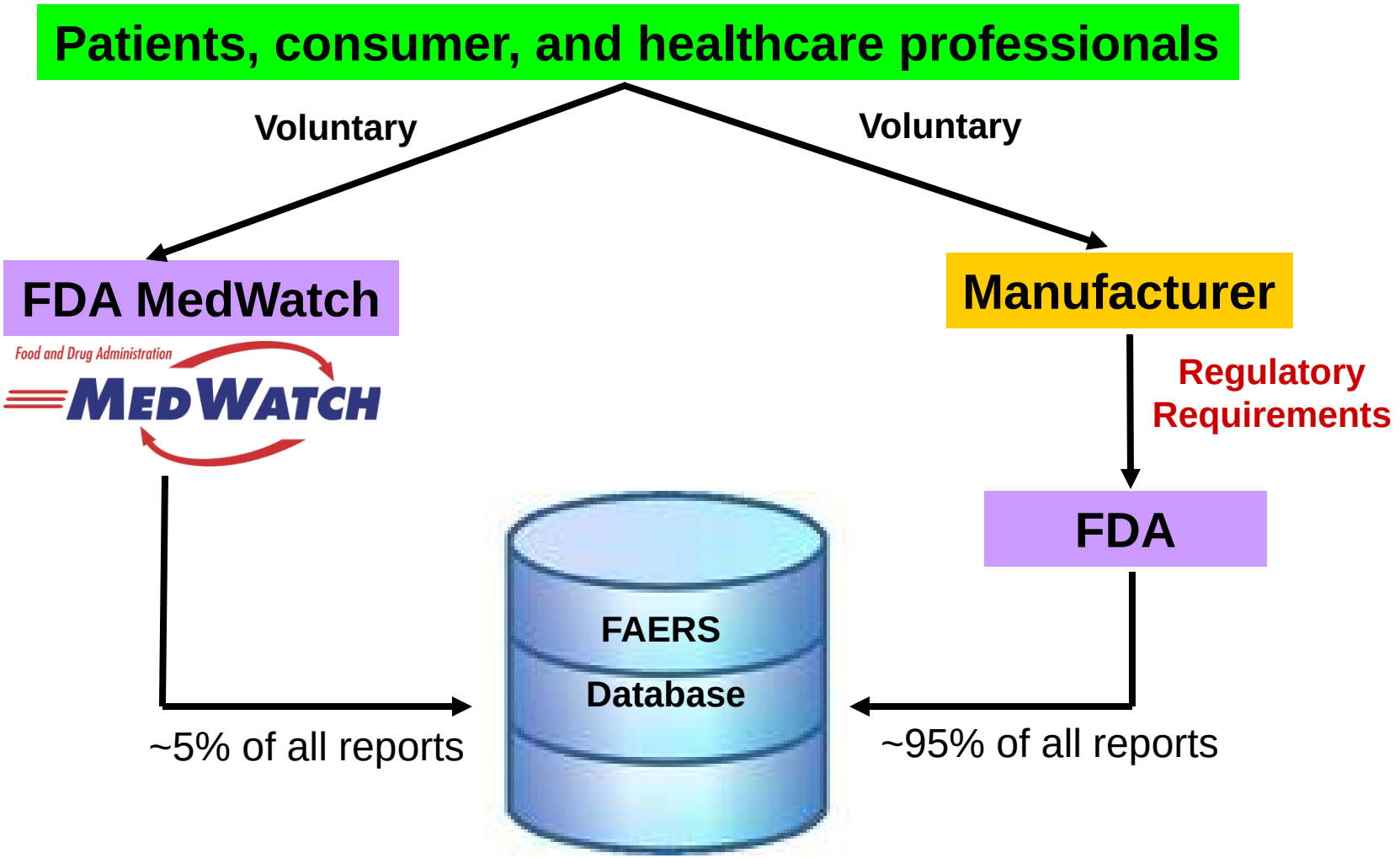
Select Postmarketing Data Sources

- 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)

Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell

Postmarket Adverse Event Reporting and FDA Adverse Event Reporting System (FAERS)

How Postmarketing Reports Get to FDA



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)

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

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

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

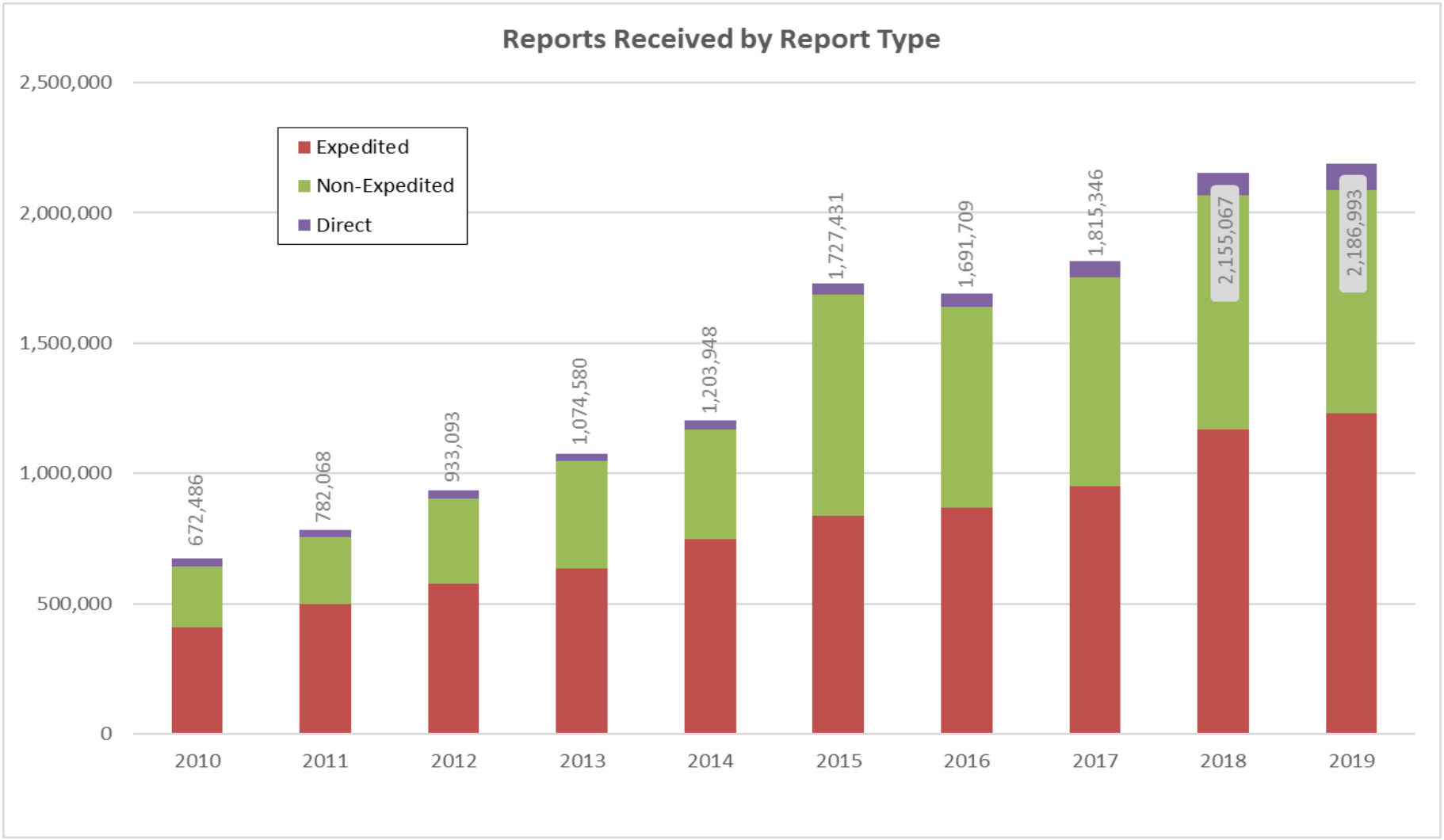
Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell

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

FAERS
FDA Adverse Event Reporting System

Number of Adverse Event Reports Entered into FAERS



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

Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell

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

U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm

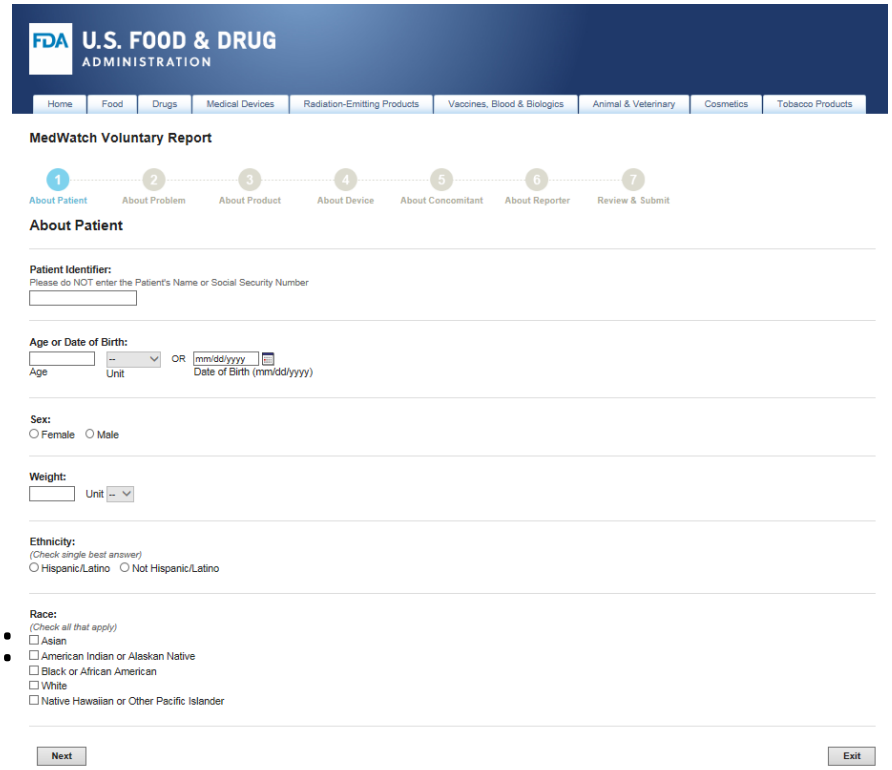
https://www.fda.gov/about-fda/fda-pharmacy-student-experiential-program/division-drug-information-webinars

How to report to MedWatch

Food and Drug Administration

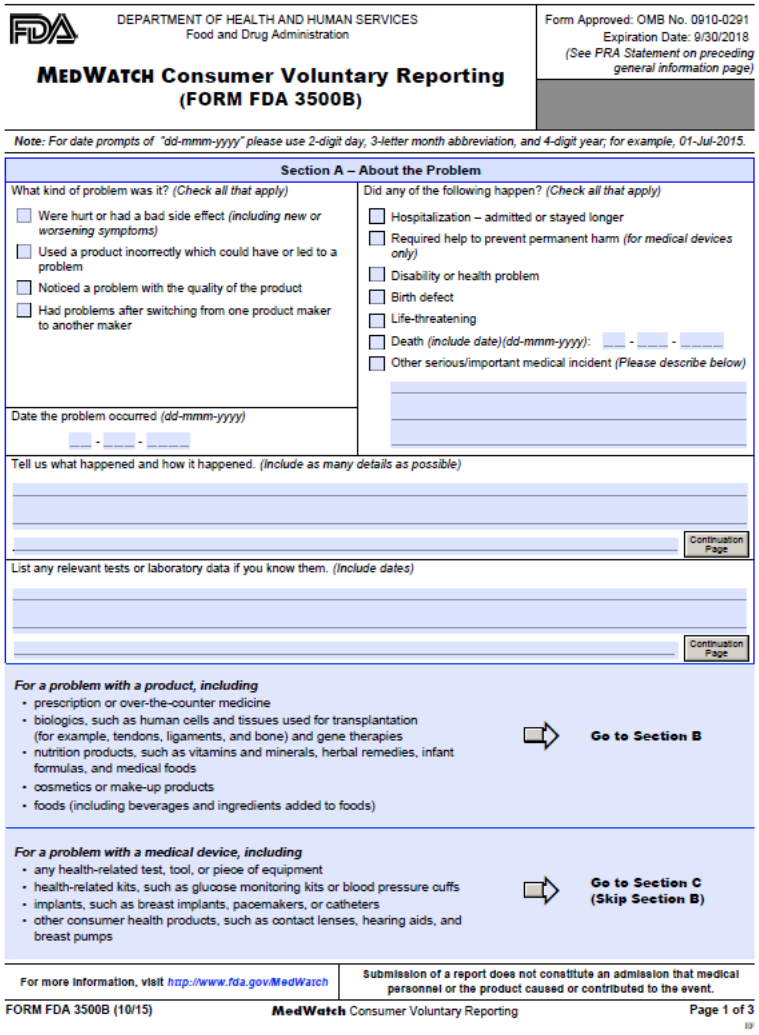
MEDWATCH

- 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



U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: https://www.fda.gov/Safety/MedWatch/default.htm

Consumer MedWatch Form



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0291
Expiration Date: 9/30/2018
(See PRA Statement on preceding general information page)

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- ☐ Were hurt or had a bad side effect *(including new or worsening symptoms)*
- ☐ Used a product incorrectly which could have or led to a problem
- ☐ Noticed a problem with the quality of the product
- ☐ Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- ☐ Hospitalization – admitted or stayed longer
- ☐ Required help to prevent permanent harm *(for medical devices only)*
- ☐ Disability or health problem
- ☐ Birth defect
- ☐ Life-threatening
- ☐ Death *(include date)(dd-mmm-yyyy)*: ___ - ____ - _____
- ☐ Other serious/important medical incident *(Please describe below)*

Date the problem occurred *(dd-mmm-yyyy)*
___ - ____ - _____

Tell us what happened and how it happened. *(Include as many details as possible)*
Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*
Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

Go to Section C (Skip Section B)

For more information, visit http://www.fda.gov/MedWatch

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

FORM FDA 3500B (10/15) **MedWatch** Consumer Voluntary Reporting Page 1 of 3

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

U.S. Food and Drug Administration. MedWatch Consumer Voluntary Reporting (FORM FDA 3500B). Available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf

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**

U.S. Food and Drug Administration. Biosimilar Product Information. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm

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)

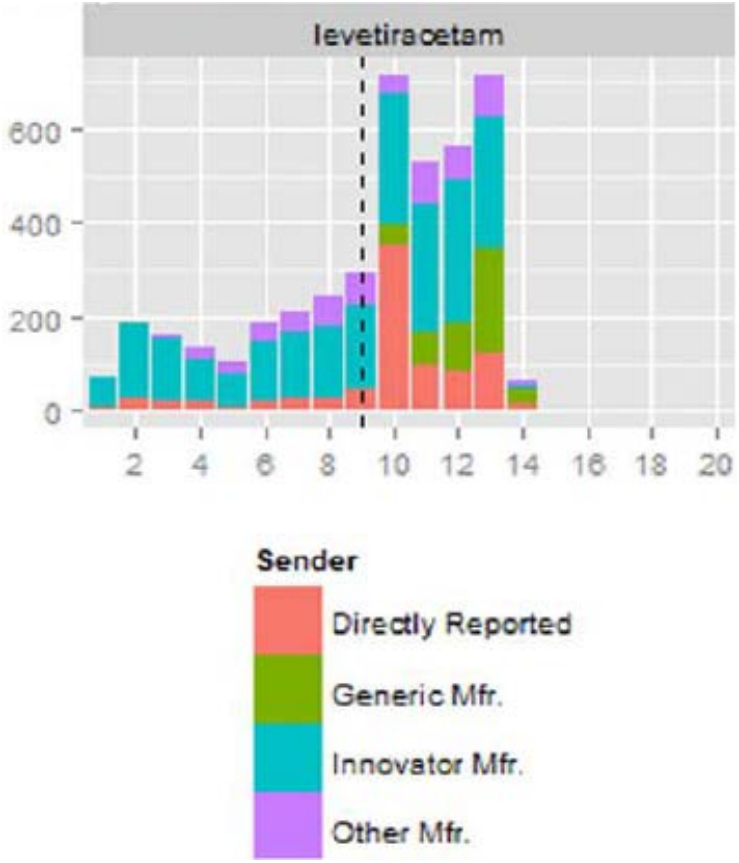
- FDA Guidance for Industry changed in 2017 to recommend that all newly approved biological products (including both the originator and biosimilar) contain a meaningless 4-letter suffix

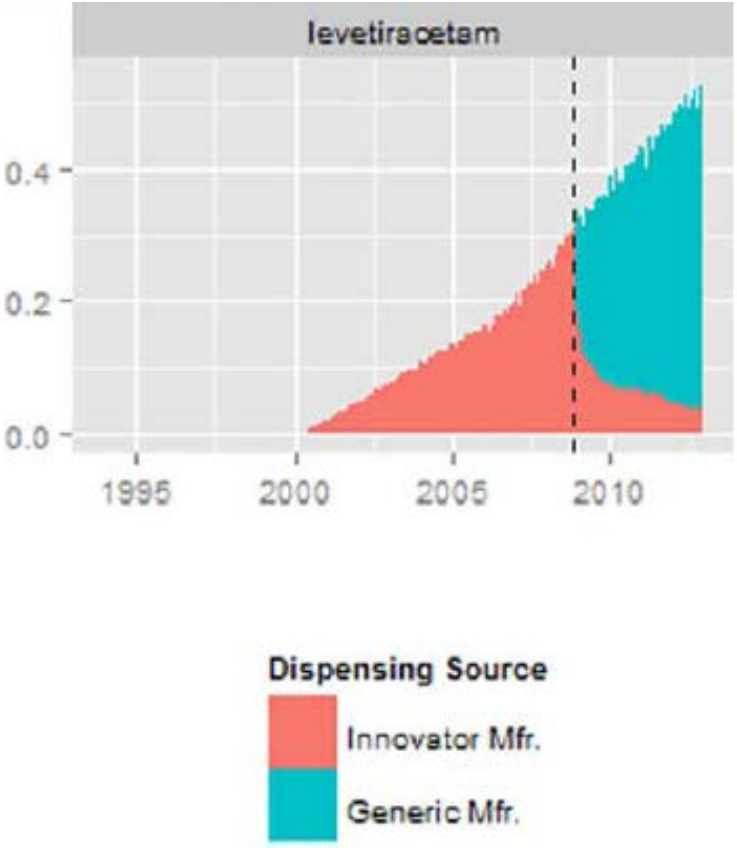
Reporting AEs For Brand vs Generic Products

- 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

Clin Pharmacol Ther. 2015 May;97(5):508-17

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

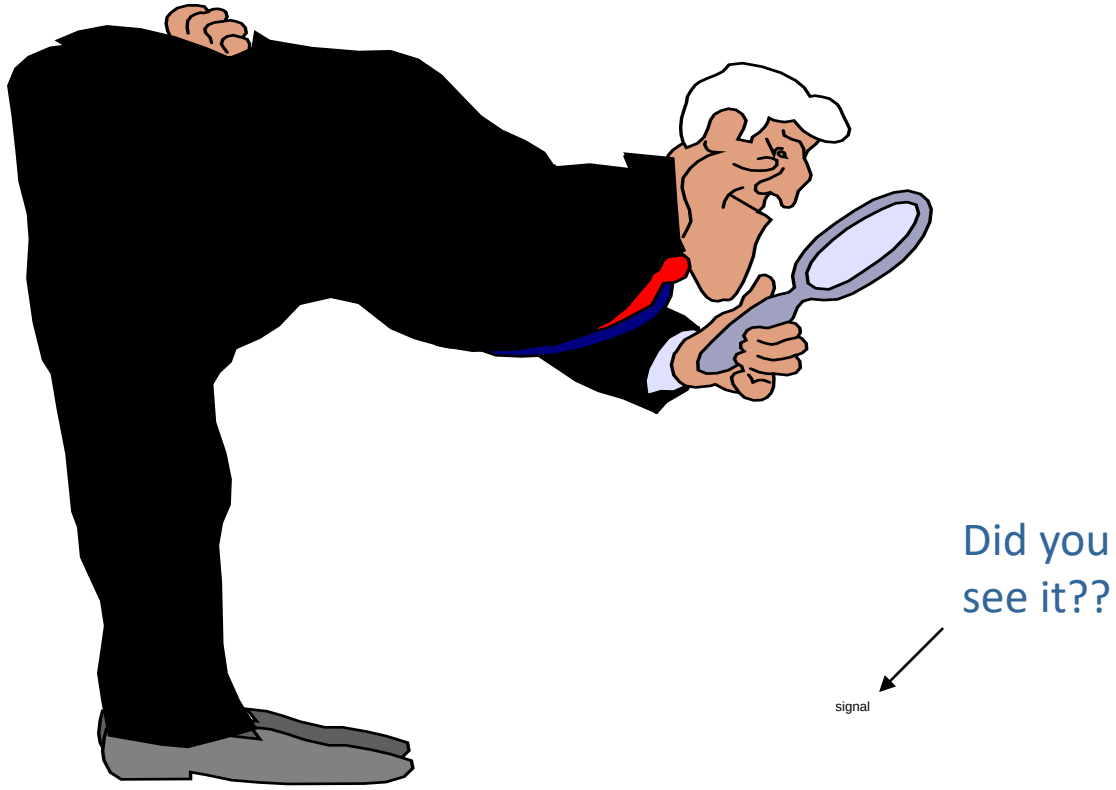
- 60-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of renal failure.
- Started Drug X at 500 mg daily on April 5, 2018 for left leg cellulitis.
- Other medications: regular insulin, glyburide, atorvastatin, and lisinopril
- Labs drawn on April 5th revealed creatinine 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

U.S. Food and Drug Administration. Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696.pdf

Safety Signal Detection

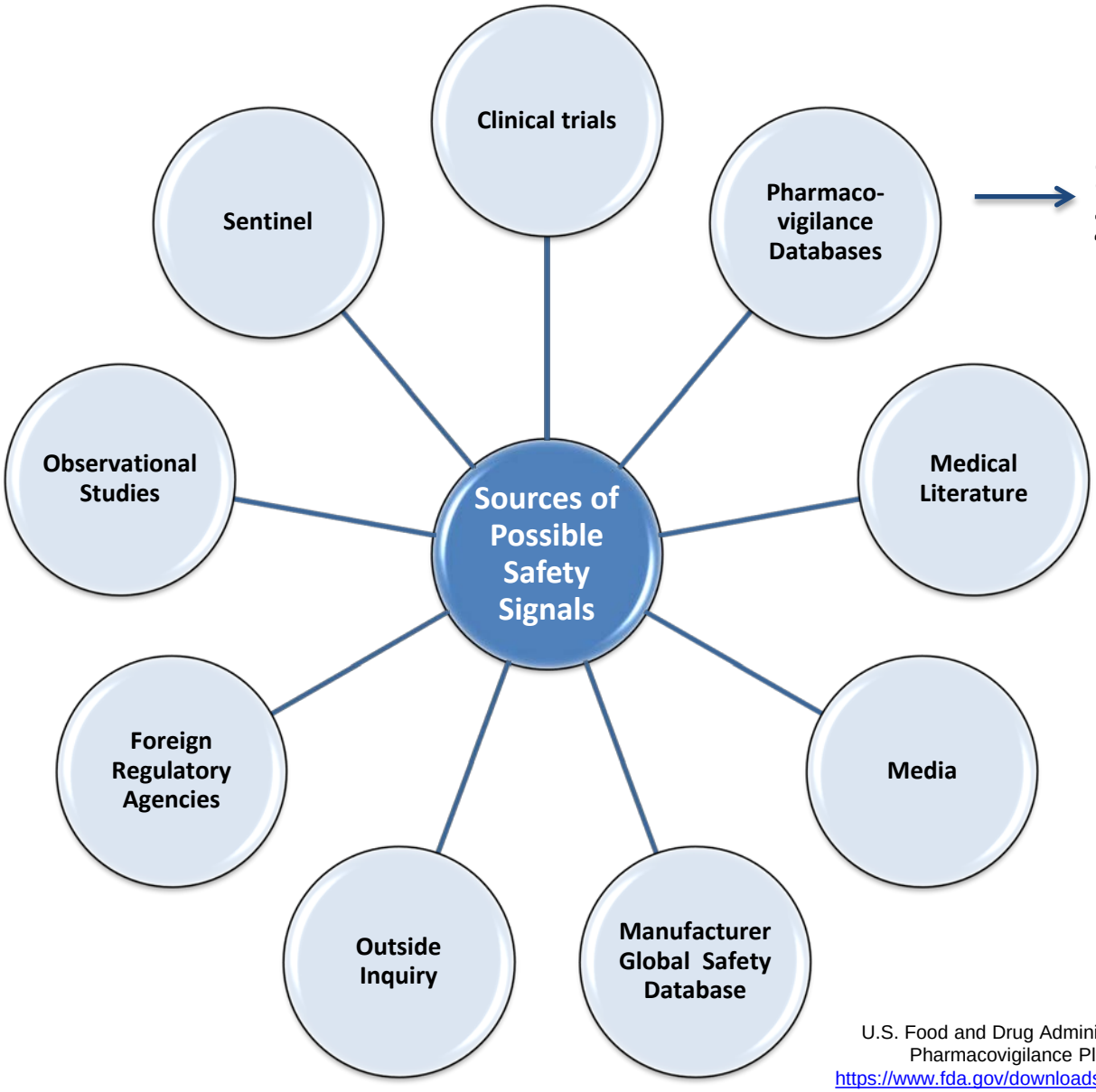


What is a Safety Signal?

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.

Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2014.

Select Sources of Possible Safety Signals

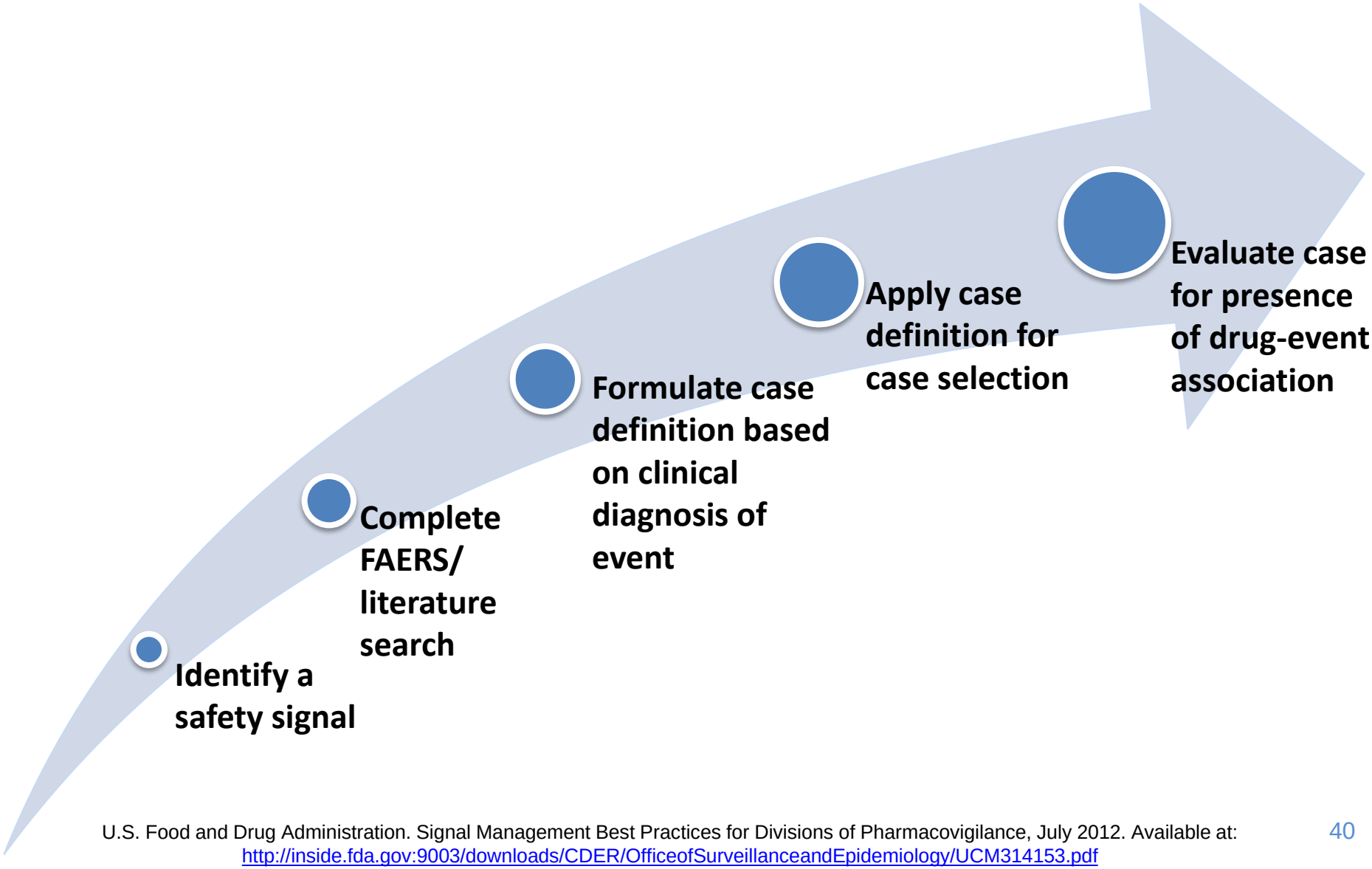


1. FAERS
2. Empirica Signal

U.S. Food and Drug Administration. Guidance for Industry – E2E Pharmacovigilance Planning, April 2005. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

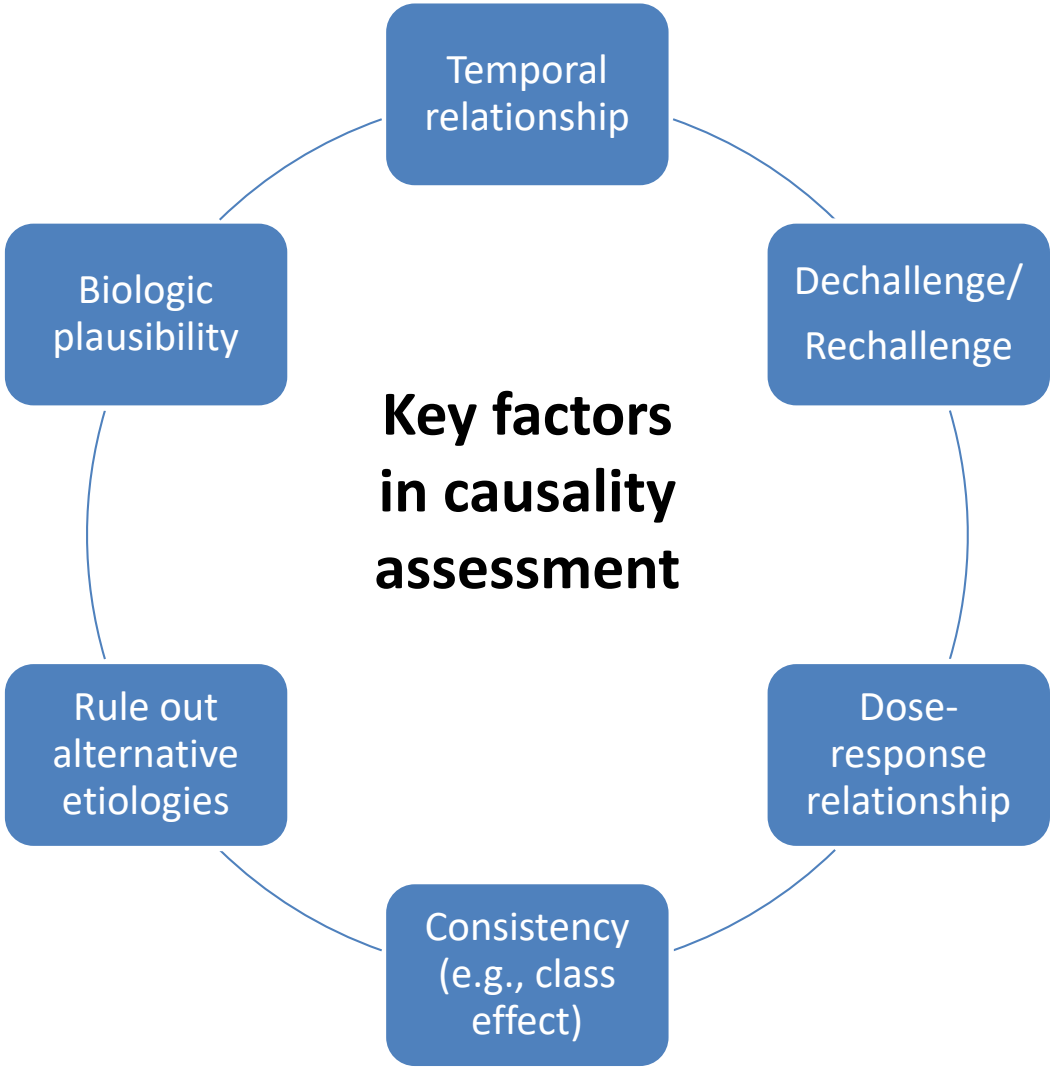
Case Series Development and Evaluation

Developing a Case Series



U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

Causality Assessment



Fedak KM, et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015;12:14.

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

U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

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)

U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

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

U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

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

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious breathing problems with seizure and nerve medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) (2019). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. (2019). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia

Safety signal examples

Loperamide and cardiac AEs

Drugs

Home › Drugs › Drug Safety and Availability

- Drug Safety and Availability
- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications
- Drug Shortages
- Postmarket Drug Safety Information for Patients and Providers
- Information by Drug Class
- Medication Errors
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Supply Chain Integrity
- Risk Evaluation and Mitigation Strategies (REMS)

FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

The FDA has issued new information about this safety issue, see the **FDA Drug Safety Communication** issued on **1-30-2018**

11/2016 & 4/2017 Update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letter and latest prescribing information for this product at: **Imodium (loperamide)** and **Imodium A-D (loperamide)**

Safety Announcement

[06-07-2016] The U.S. Food and Drug Administration (FDA) is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide (see Examples of Drugs that Can Potentially Interact with Loperamide).

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. We continue to evaluate this safety issue and will determine if additional FDA actions are needed.

- 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

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

Loperamide and cardiac AEs

SCIENCE AND PRACTICE

Journal of the American Pharmacists Association 57 (2017) S63–S67

Contents lists available at ScienceDirect

Journal of the American Pharmacists Association

journal homepage: www.japha.org

RESEARCH NOTES

Adverse event detection using the FDA post-marketing drug safety surveillance system: Cardiotoxicity associated with loperamide abuse and misuse

Kimberley A. Swank*, Eileen Wu, Cindy Kortepeter, Jana McAninch, Robert L. Levin

ARTICLE INFO

Article history:
Received 26 August 2016
Accepted 18 November 2016

ABSTRACT

Objective: The purpose of this investigation was to identify and cl
reports of cardiotoxicity, including torsades de pointes (TdP), assoc
Methods: We searched the U.S. Food and Drug Administration Ad
tem (FAERS) database for post-marketing reports of serious cardiac
with loperamide use from December 28, 1976 (U.S. drug approval d
2015. We also conducted a Pubmed and Google Scholar search to id
reports of cardiotoxicity associated with loperamide in the r
February 11, 2016.
Results: Forty-eight cases of serious cardiac adverse events assoc
composed the case series. The most frequently reported cardiac ad
(n = 24), cardiac arrest (n = 13), QT-interval prolongation (n = 1
(n = 10), and TdP (n = 7). There were 10 cases that resulted in deat
commonly reported reasons for use can be characterized as drug al
treatment (n = 17). More than one-half of the 48 cases were repo
drug abuse cases, the median daily dose was 250 mg (range 70 m
occurred as early as 6 hours after a dose and as long as 18 month
amide. Thirteen of the 22 cases reported using loperamide for eu
and 9 reported use to prevent opioid withdrawal symptoms.

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 4, 2017

ISSN 2405-500X/$36.00

Letters

TO THE EDITOR

Labeling and Drug Safety Communication Approaches to Loperamide Abuse

We read with great interest the loperamide study of Klein et al. (1). The U.S. Food and Drug Administration (FDA) Division of Pharmacovigilance recently reviewed 48 cases of torsades de pointes and other serious cardiac adverse events with loperamide use received through the FDA Adverse Event Reporting System database (2). Thirty-one of these cases resulted in hospitalizations, and 10 patients died. More than one-half of the 48 cases were reported after 2010, coinciding with increased recreational abuse. Loperamide median dose was 250 mg (range 70 to 1600 mg) for abusers in our approaches. FDA will continue to monitor this issue and take the steps necessary to help prevent the abuse of loperamide.

*Daniel Woronow, MD
Kimberley A. Swank, PharmD
Eileen Wu, PharmD
Cindy Kortepeter, PharmD
Robert L. Levin, MD

*Division of Pharmacovigilance
Office of Surveillance and Epidemiology
Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 3475
Silver Spring, Maryland 20993
E-mail: Daniel.Woronow@fda.hhs.gov

http://dx.doi.org/10.1016/j.jacep.2017.02.011

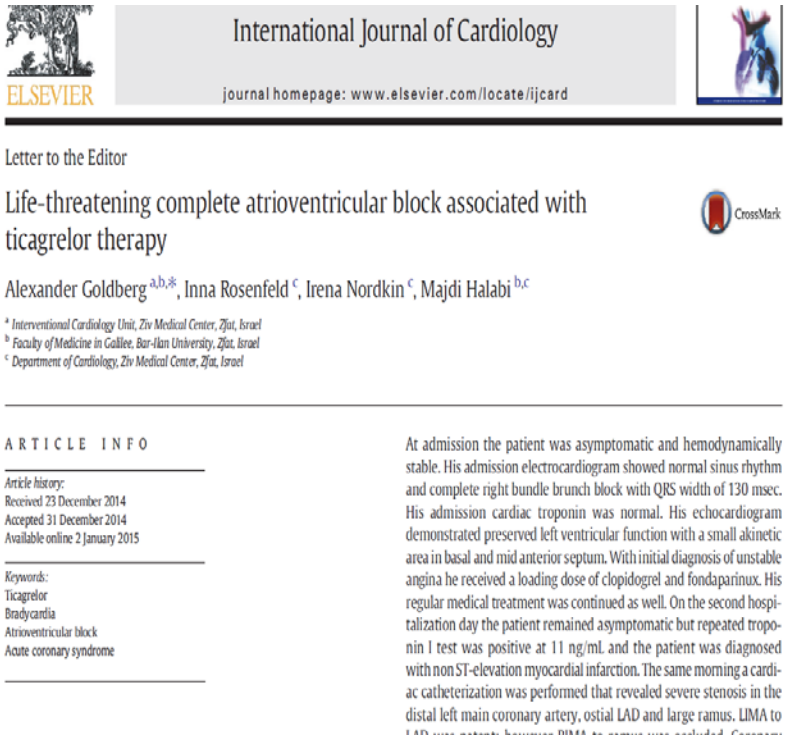
Published by Elsevier on behalf of the American College of Cardiology Foundation

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. No independent funding, grants, contracts, or other forms of financial support have been used in preparation of this manuscript. The views expressed are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

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



ELSEVIER

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Life-threatening complete atrioventricular block associated with ticagrelor therapy

Alexander Goldberg [a,b,*], Inna Rosenfeld [c], Irena Nordkin [c], Majdi Halabi [b,c]

[a] Interventional Cardiology Unit, Ziv Medical Center, Zfat, Israel
[b] Faculty of Medicine in Galilee, Bar-Ilan University, Zfat, Israel
[c] Department of Cardiology, Ziv Medical Center, Zfat, Israel

ARTICLE INFO

Article history:
Received 23 December 2014
Accepted 31 December 2014
Available online 2 January 2015

Keywords:
Ticagrelor
Bradycardia
Atrioventricular block
Acute coronary syndrome

At admission the patient was asymptomatic and hemodynamically stable. His admission electrocardiogram showed normal sinus rhythm and complete right bundle brunch block with QRS width of 130 msec. His admission cardiac troponin was normal. His echocardiogram demonstrated preserved left ventricular function with a small akinetic area in basal and mid anterior septum. With initial diagnosis of unstable angina he received a loading dose of clopidogrel and fondaparinux. His regular medical treatment was continued as well. On the second hospitalization day the patient remained asymptomatic but repeated troponin I test was positive at 11 ng/mL and the patient was diagnosed with non ST-elevation myocardial infarction. The same morning a cardiac catheterization was performed that revealed severe stenosis in the distal left main coronary artery, ostial LAD and large ramus. LIMA to

- 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

Goldberg A, et al. Life-threatening complete atrioventricular block associated with ticagrelor therapy. Int J Cardiol. 2015 Mar 1;182:379-80.

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

Goldberg A, et al. Life-threatening complete atrioventricular block associated with ticagrelor therapy. Int J Cardiol. 2015 Mar 1;182:379-80.

Ticagrelor Labeling

- WARNINGS AND PRECAUTIONS

  5.5 Bradyarrythmias

  Ticagrelor can cause ventricular pauses [see Adverse Reactions (6.1)]. Bradyarrythmias including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd 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 bradyarrythmias with ticagrelor

Brilinta (ticagrelor) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022433s022lbl.pdf. Updated March 9, 2018.

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

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

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

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA

FDA USE ONLY

Triage unit
sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
JG In confidence		☐ Female ☒ Male	____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☒ Death: 11/7/2012 *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
   ☐ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11/7/2012	11/14/2012

5. Describe Event, Problem or Product Use Error

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.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Drug X
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1		
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. Diagnosis or Reason for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)* 7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
Name:
Address: A. Pharmacist, A. University Hospital
City: State: ZIP:

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☒ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

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

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA

FDA USE ONLY
Triage unit
sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
JG In confidence	69 yo	☐ Female ☒ Male	189 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☒ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☒ Death: 11/7/2012 *(mm/dd/yyyy)*
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   ☐ Disability or Permanent Damage
   ☐ Congenital Anomaly/Birth Defect
   ☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
11/7/2012	11/14/2012

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…

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

		Dose or Amount	Frequency	Route
#1	Name: Drug X 125mg, XX Pharmacy Strength: Manufacturer:	125mg	once	IV
#2	Name: Strength: Manufacturer:			

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
   #1 10/15/12
   #2

4. Diagnosis or Reason for Use *(Indication)*
   #1 Back pain
   #2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☒ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1	#1	
#2	#2	

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot # 23557	5. Operator of Device ☐ Health Professional
Catalog #	Expiration Date *(mm/dd/yyyy)* 10/19/2012	☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. If Implanted, Give Date *(mm/dd/yyyy)*
7. If Explanted, Give Date *(mm/dd/yyyy)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

Please see accompanying file

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
   Name: Dr. Heath Filie
   Address: Clinical Pharmacist, Pain Clinic
   City: Pennsylvania State: ZIP:

Phone #	E-mail
(717) 555-8899	pills4U@yahoo.com

2. Health Professional?	3. Occupation	4. Also Reported to:
☒ Yes ☐ No	Pharmacist	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (1/09)

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

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?


FDA
U.S. FOOD & DRUG
ADMINISTRATION