FDA Drug Topics: An Overview of Pharmacovigilance in the Center for Drug Evaluation and Research (CDER)

March 26, 2019

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Division of Pharmacovigilance
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

FDA

Office of the Commissioner

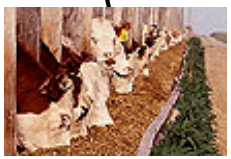
Office of Operations

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

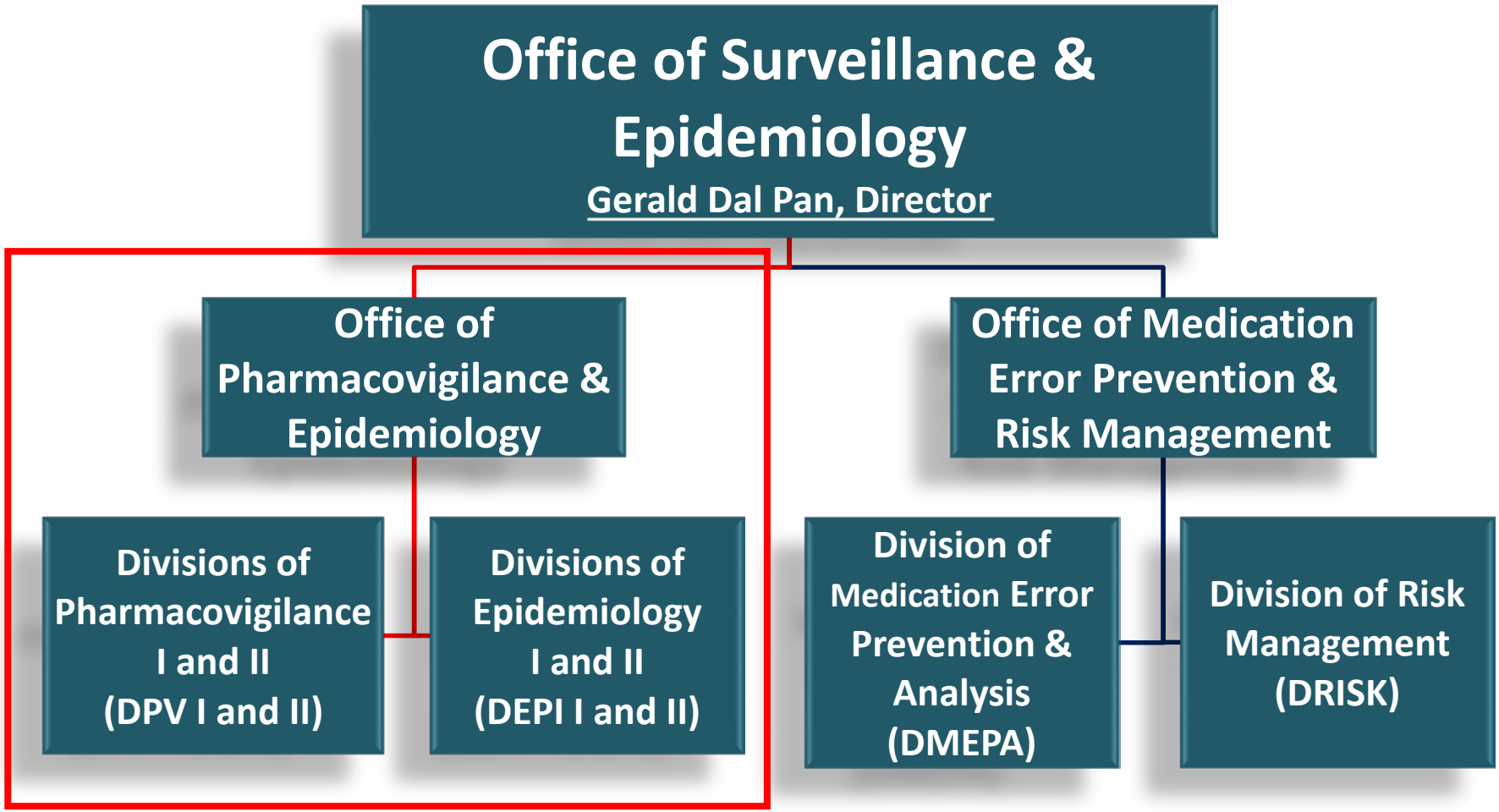
Office of New Drugs

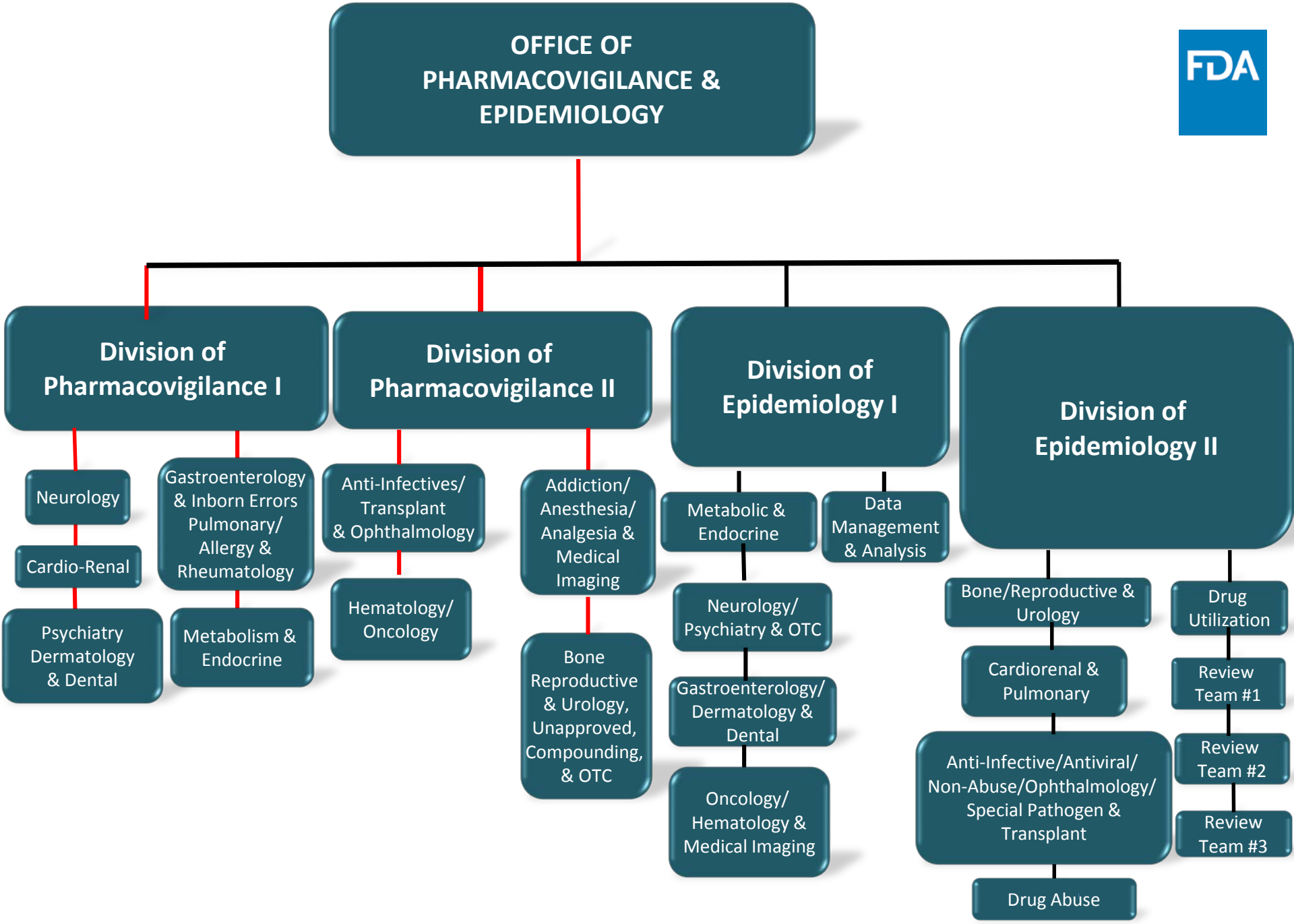
Office of Generic Drugs

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 (DRISK)


OFFICE OF PHARMACOVIGILANCE & EPIDEMIOLOGY
Division of Pharmacovigilance I
Neurology
Cardio-Renal
Psychiatry Dermatology & Dental
Gastroenterology & Inborn Errors Pulmonary/ Allergy & Rheumatology
Metabolism & Endocrine
Division of Pharmacovigilance II
Anti-Infectives/ Transplant & Ophthalmology
Hematology/ Oncology
Addiction/ Anesthesia/ Analgesia & Medical Imaging
Bone Reproductive & Urology, 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

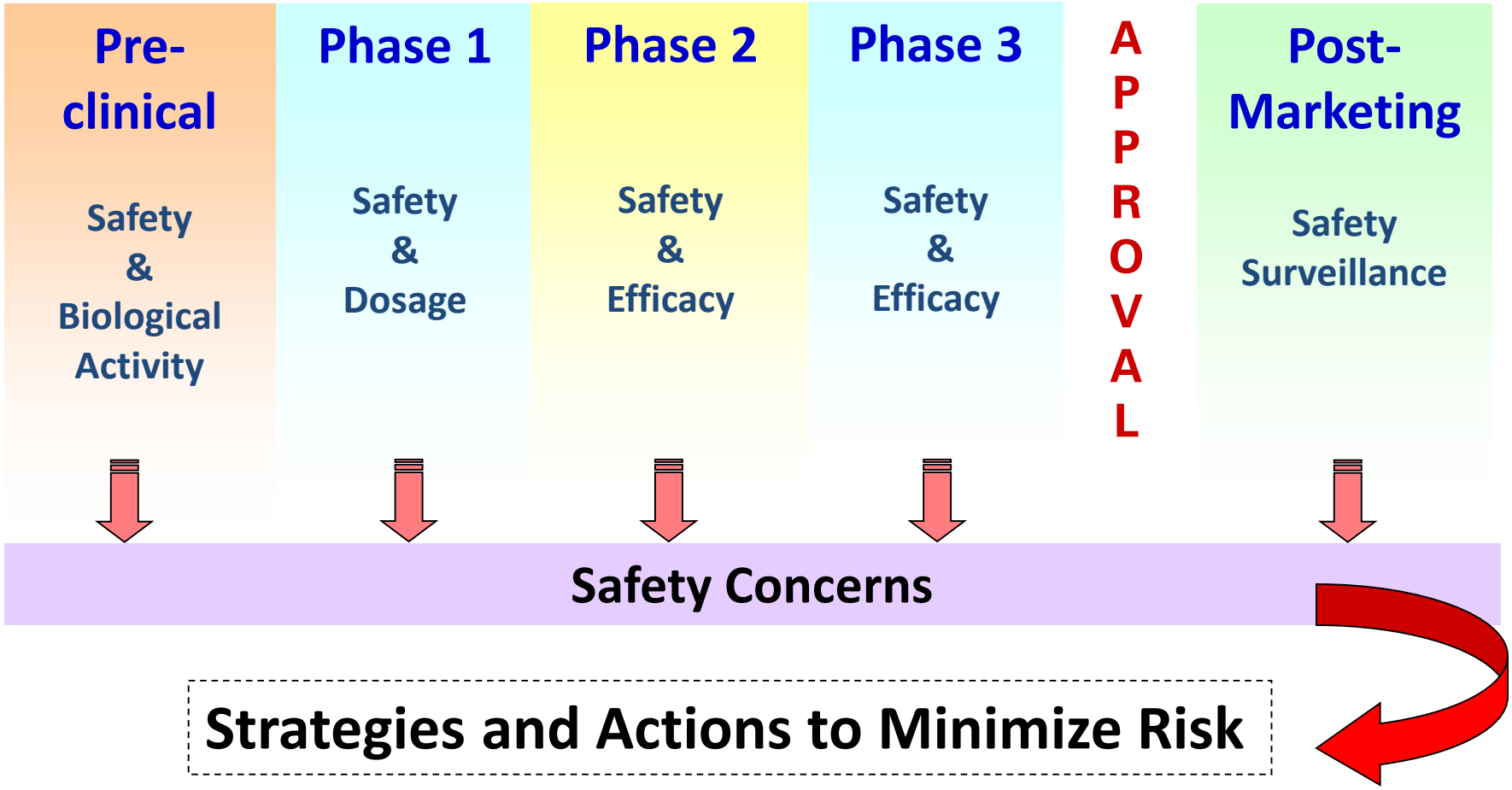
Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

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
Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

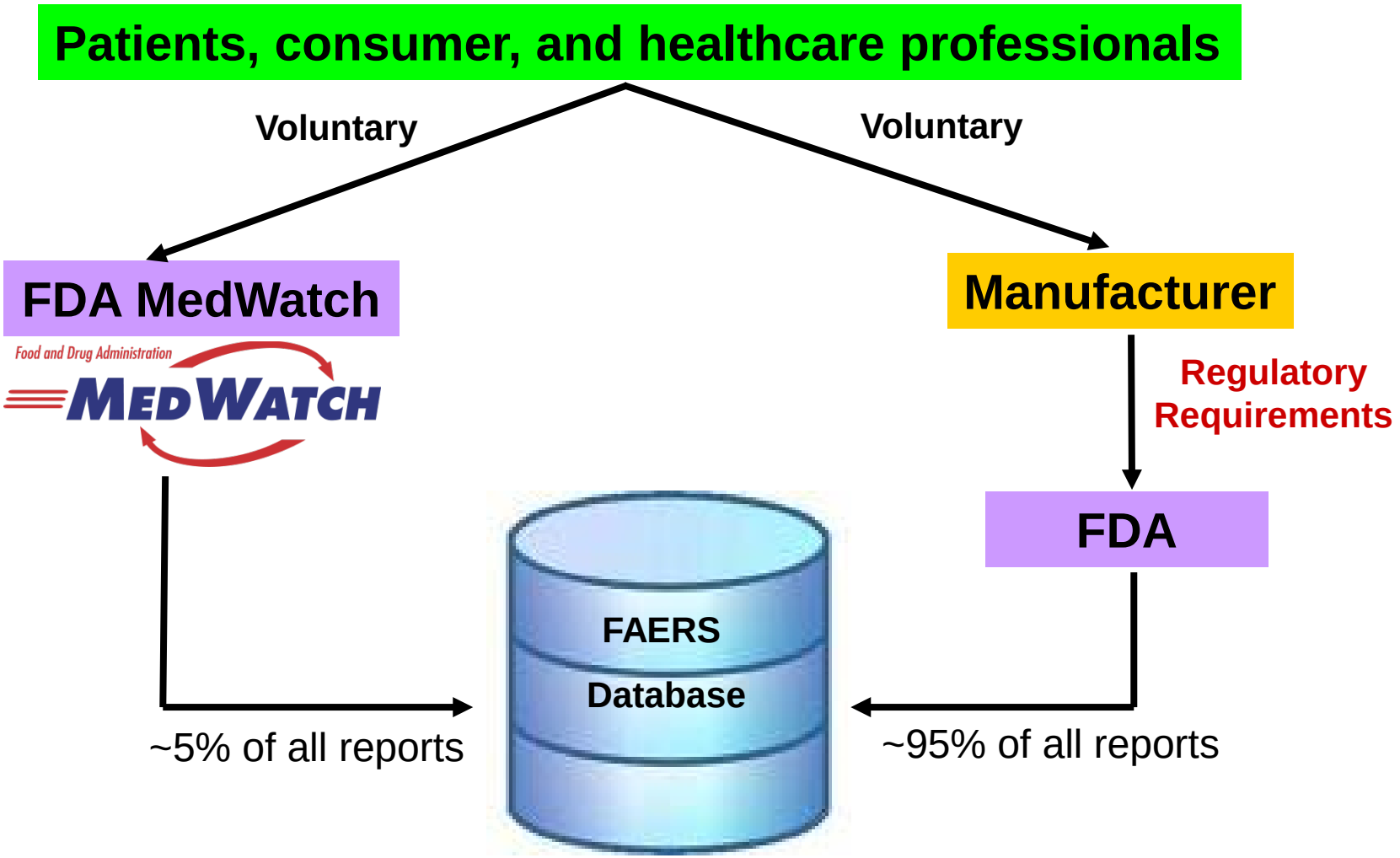
Select Postmarketing Data Sources

- 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)

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm.

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 events 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

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

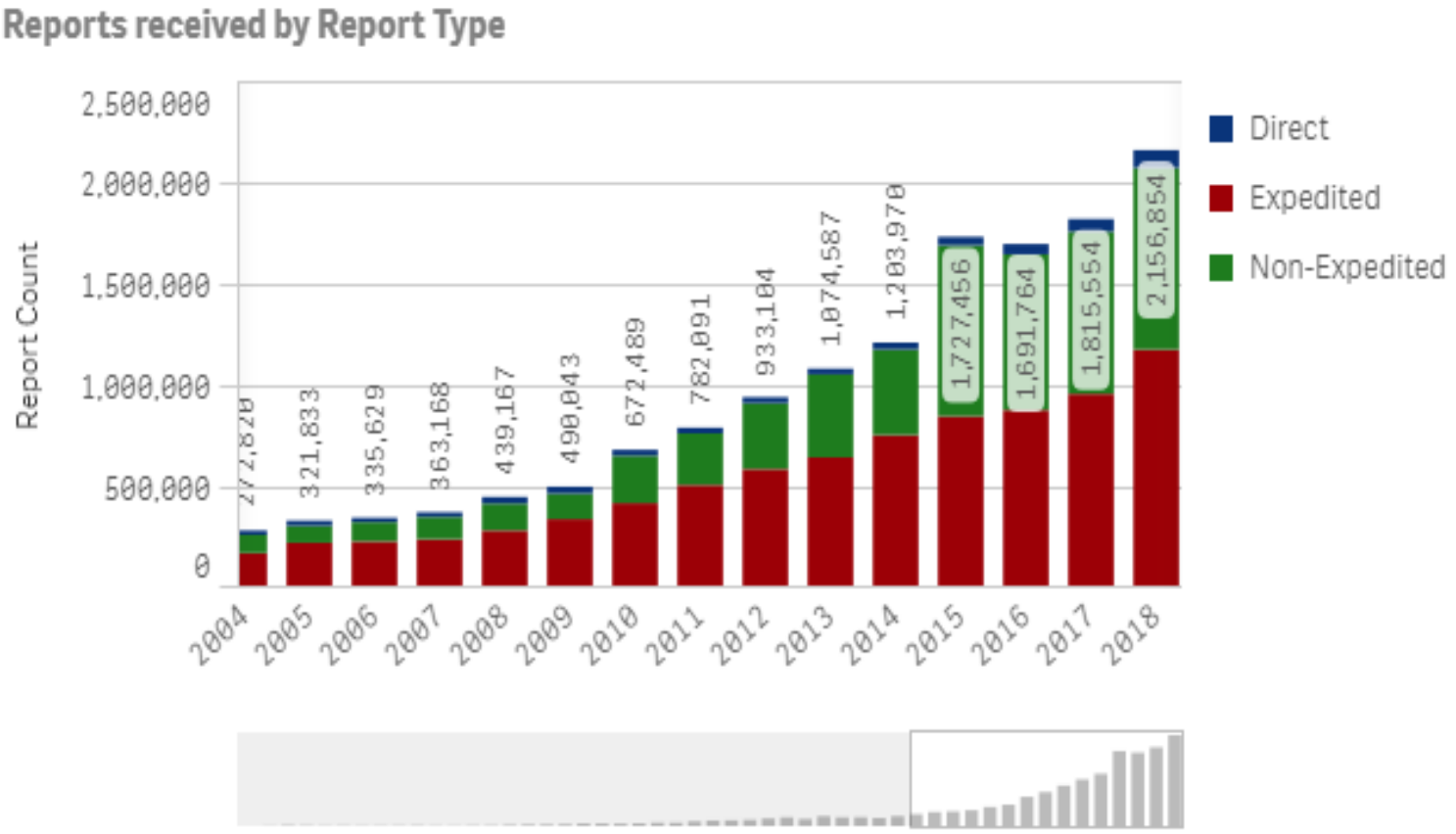
FDA Adverse Event Reporting System

- 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)*

FDA Adverse Event Reporting System

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

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

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

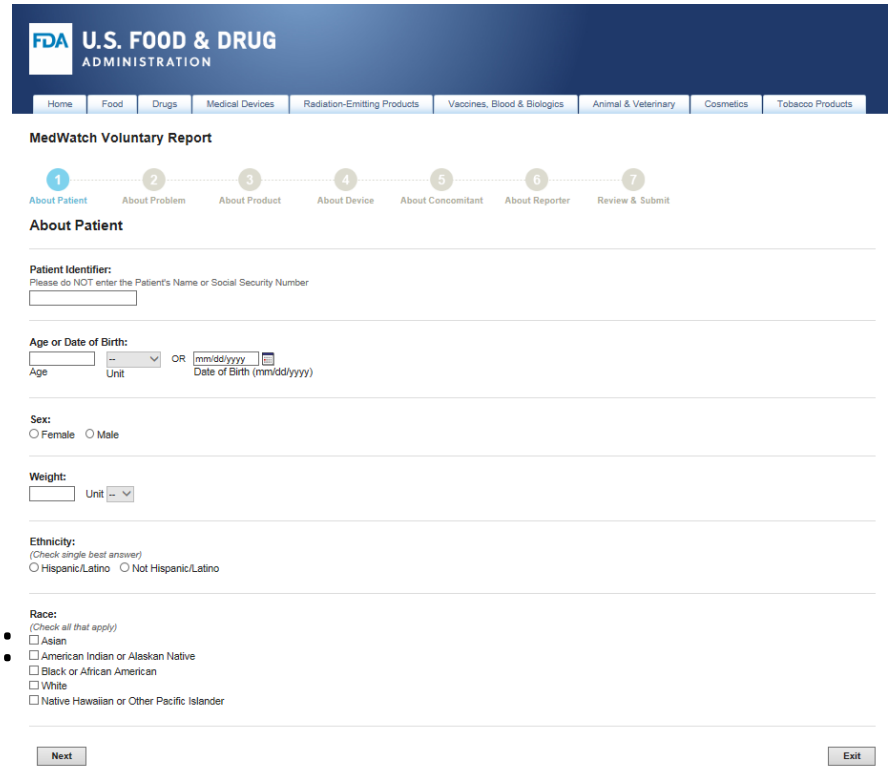
U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm

How to report to MedWatch

Food and Drug Administration

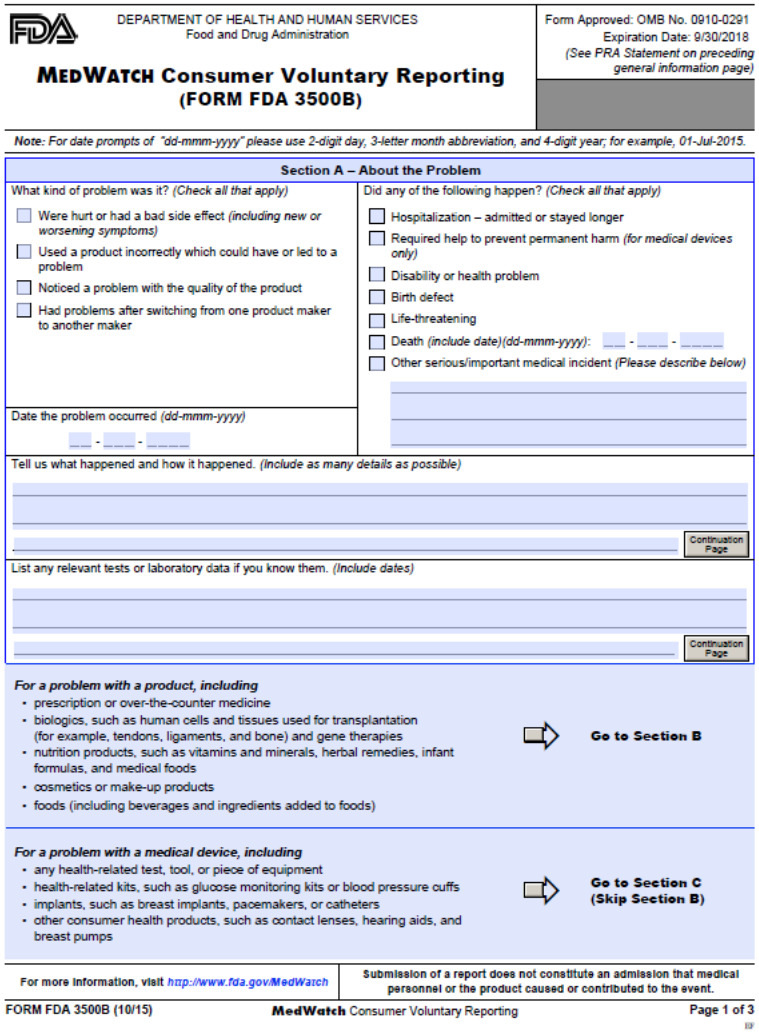
MEDWATCH

- 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

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

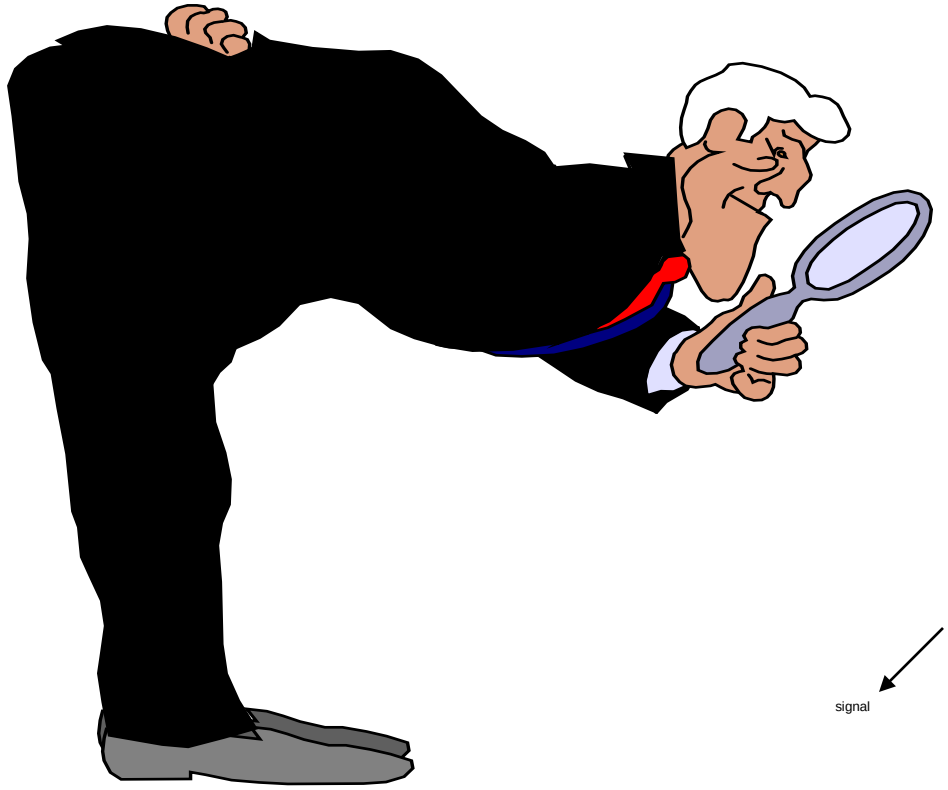
- 2 weeks after starting Drug X patient presented to ER with 2 day history of generalized rash on hands, face, and feet, weakness, arthralgia, and fever.
- On exam, she was noted to have conjunctival hyperemia, multiple-erythema-like eruptions with blisters on the skin that covered 10 % or more of the 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

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



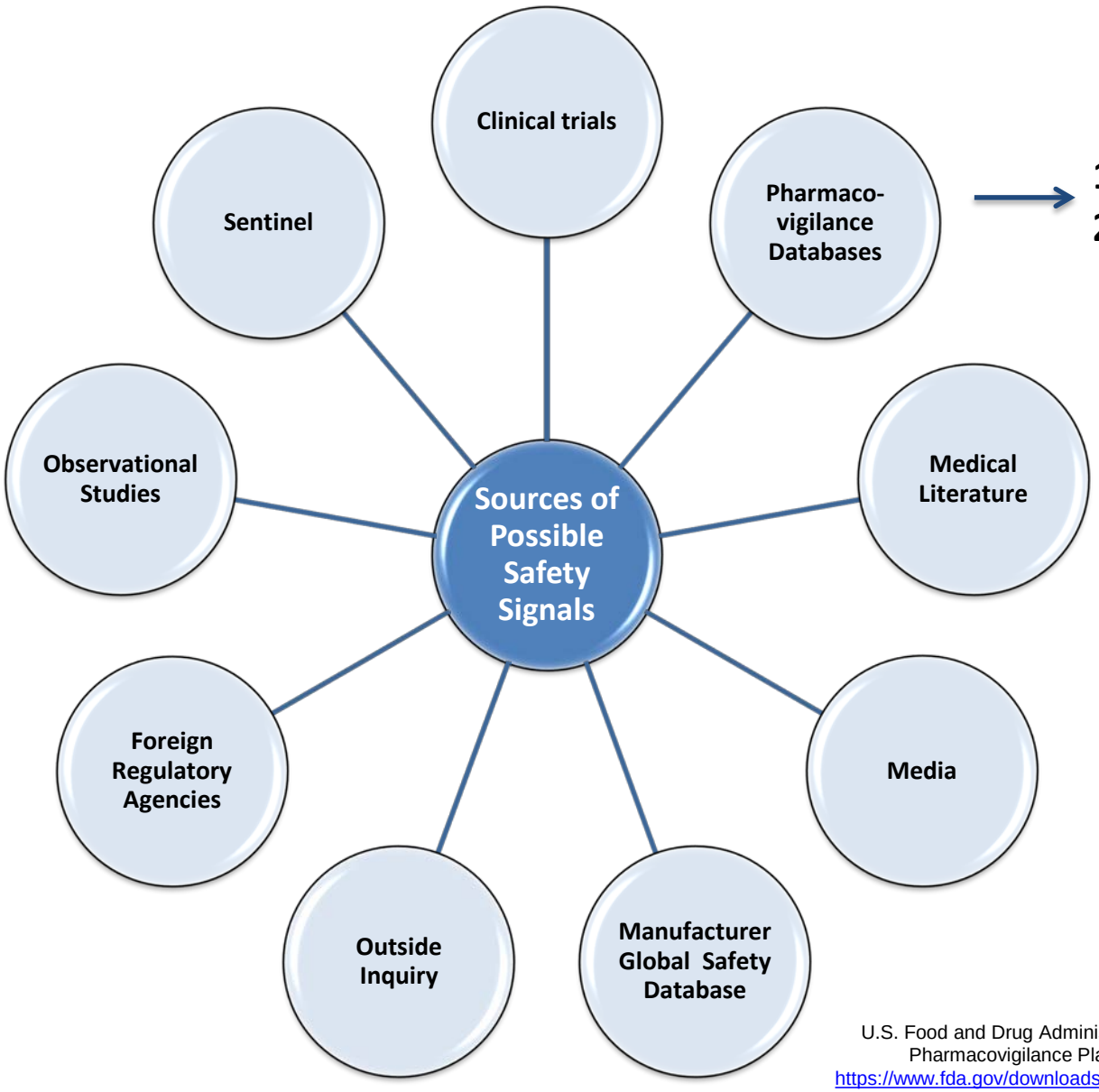
What is a Safety Signal?

- 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

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

Select Sources of Possible Safety Signals



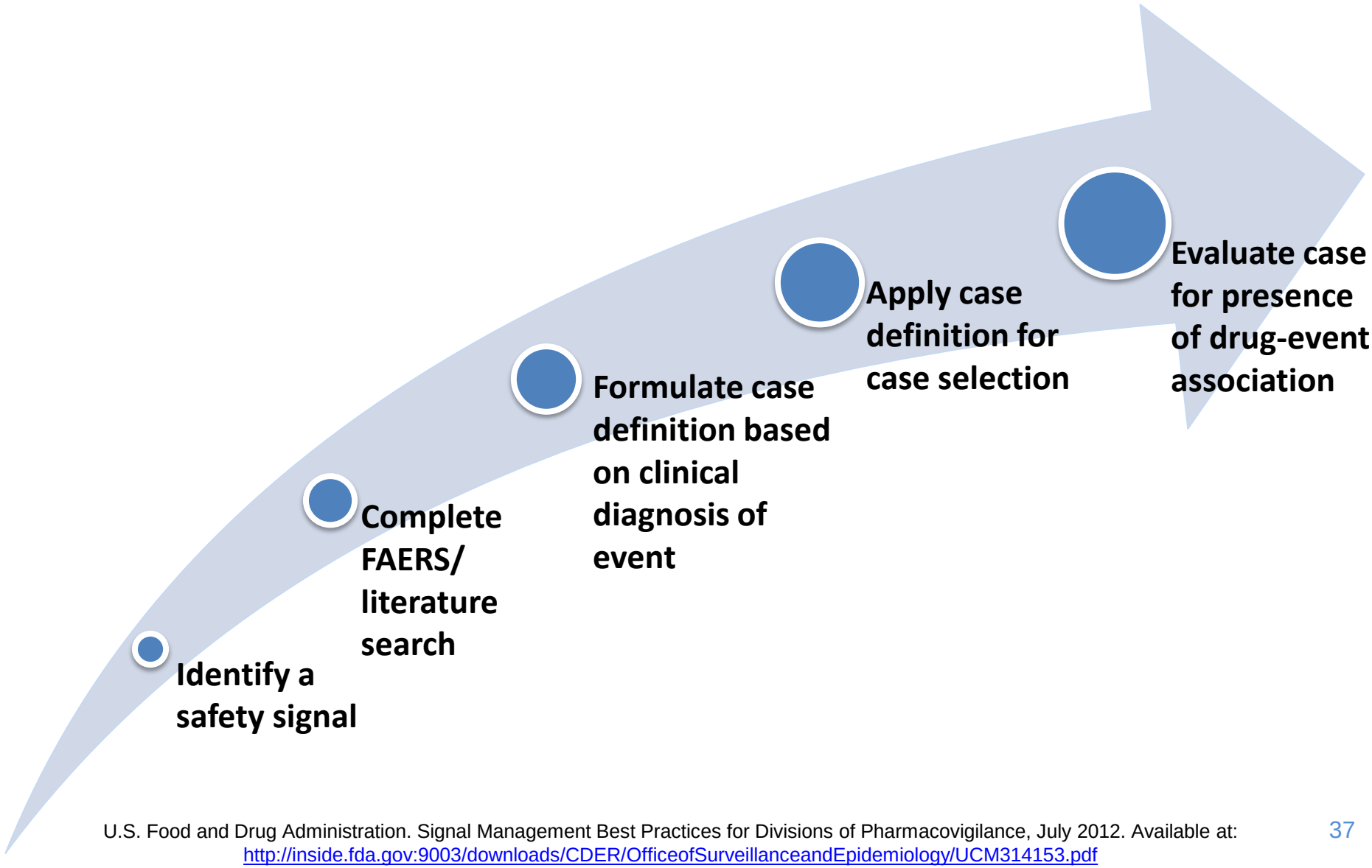
U.S. Food and Drug Administration. Guidance for Industry – E2E Pharmacovigilance Planning, April 2005. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

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)

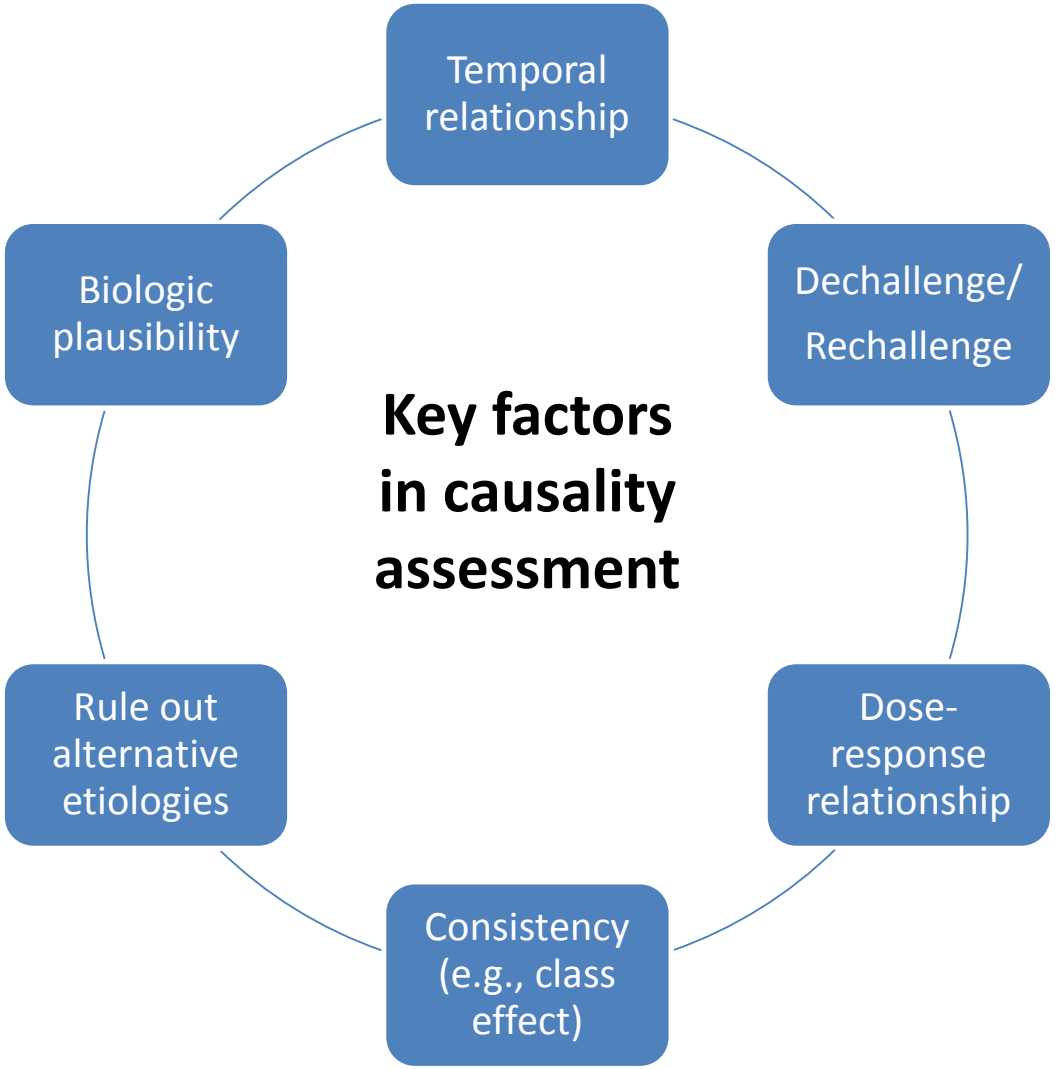
Case Series Development and Evaluation

Developing a Case Series



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)
- 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 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)

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. Viberzi (eluxadoline): Drug Safety Communication - Increased Risk of Serious Pancreatitis In Patients Without A Gallbladder (2017). Available at: https://www.fda.gov/drugs/drugsafety/ucm546154.htm
U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate . (2017). Available at: https://www.fda.gov/Drugs/DrugSafety/ucm530975.htm

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
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- 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

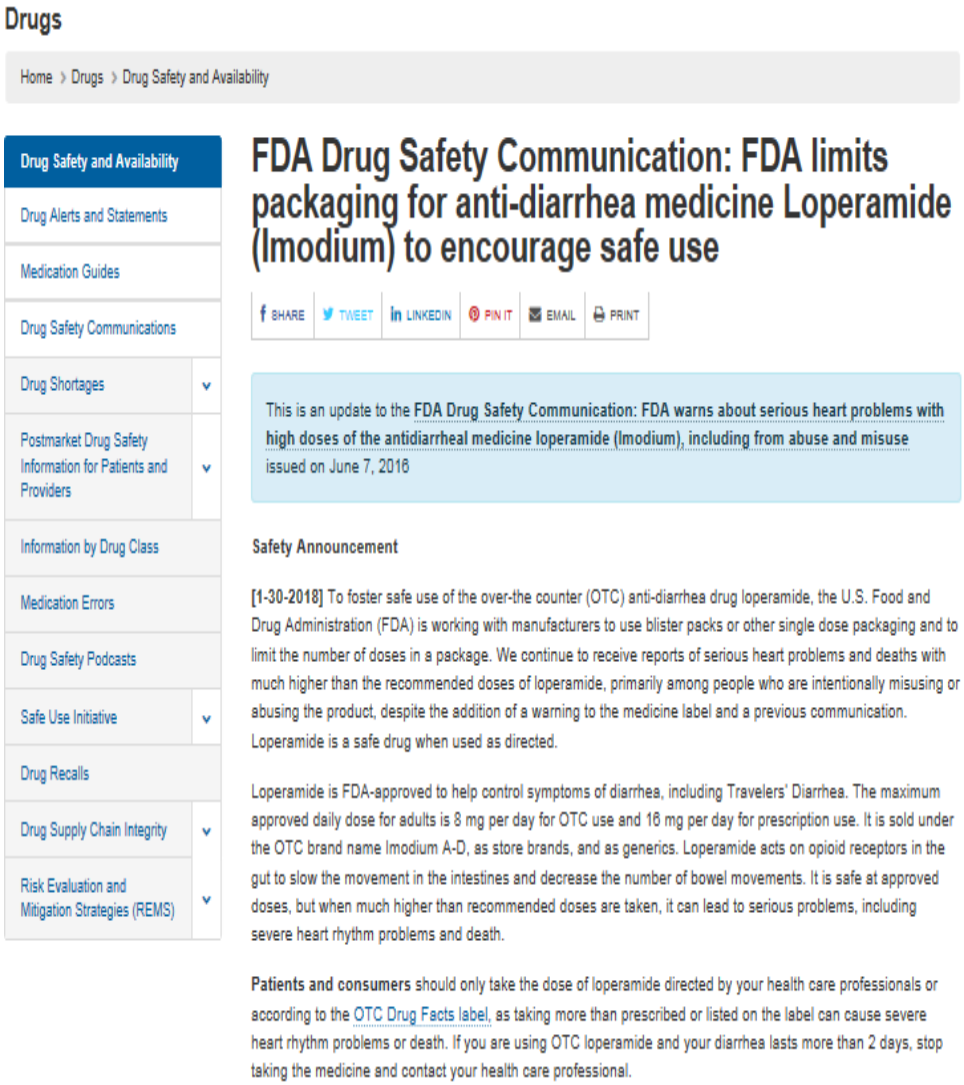
[06-07-2016] The U.S. Food and Drug Administration (FDA) is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead 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



Drugs

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Drug Recalls
Drug Supply Chain Integrity
Risk Evaluation and Mitigation Strategies (REMS)

FDA Drug Safety Communication: FDA limits packaging for anti-diarrhea medicine Loperamide (Imodium) to encourage safe use

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

This is an update to the FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse issued on June 7, 2016

Safety Announcement

[1-30-2018] To foster safe use of the over-the counter (OTC) anti-diarrhea drug loperamide, the U.S. Food and Drug Administration (FDA) is working with manufacturers to use blister packs or other single dose packaging and to limit the number of doses in a package. We continue to receive reports of serious heart problems and deaths with much higher than the recommended doses of loperamide, primarily among people who are intentionally misusing or abusing the product, despite the addition of a warning to the medicine label and a previous communication. Loperamide is a safe drug when used as directed.

Loperamide is FDA-approved to help control symptoms of diarrhea, including Travelers' Diarrhea. The maximum approved daily dose for adults is 8 mg per day for OTC use and 16 mg per day for prescription use. It is sold under the OTC brand name Imodium A-D, as store brands, and as generics. Loperamide acts on opioid receptors in the gut to slow the movement in the intestines and decrease the number of bowel movements. It is safe at approved doses, but when much higher than recommended doses are taken, it can lead to serious problems, including severe heart rhythm problems and death.

Patients and consumers should only take the dose of loperamide directed by your health care professionals or according to the OTC Drug Facts label, as taking more than prescribed or listed on the label can cause severe heart rhythm problems or death. If you are using OTC loperamide and your diarrhea lasts more than 2 days, stop taking the medicine and contact your health care professional.

- 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 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

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RESEARCH NOTES

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

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ARTICLE INFO

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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

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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.

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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

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)*
   ☐ 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

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