U.S. FOOD & DRUG ADMINISTRATION

FDA Drug Topics: FDA's Role in Postmarketing Drug Safety Surveillance

Tiffany Kim, PharmD
Safety Evaluator

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

Objectives

- Describe FDA's drug safety surveillance system at the Center for Drug Evaluation and Research (CDER)
- Explain the MedWatch Program and how you can have an impact on signal detection
- Discuss how adverse event reports are collected and analyzed
- Demonstrate 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

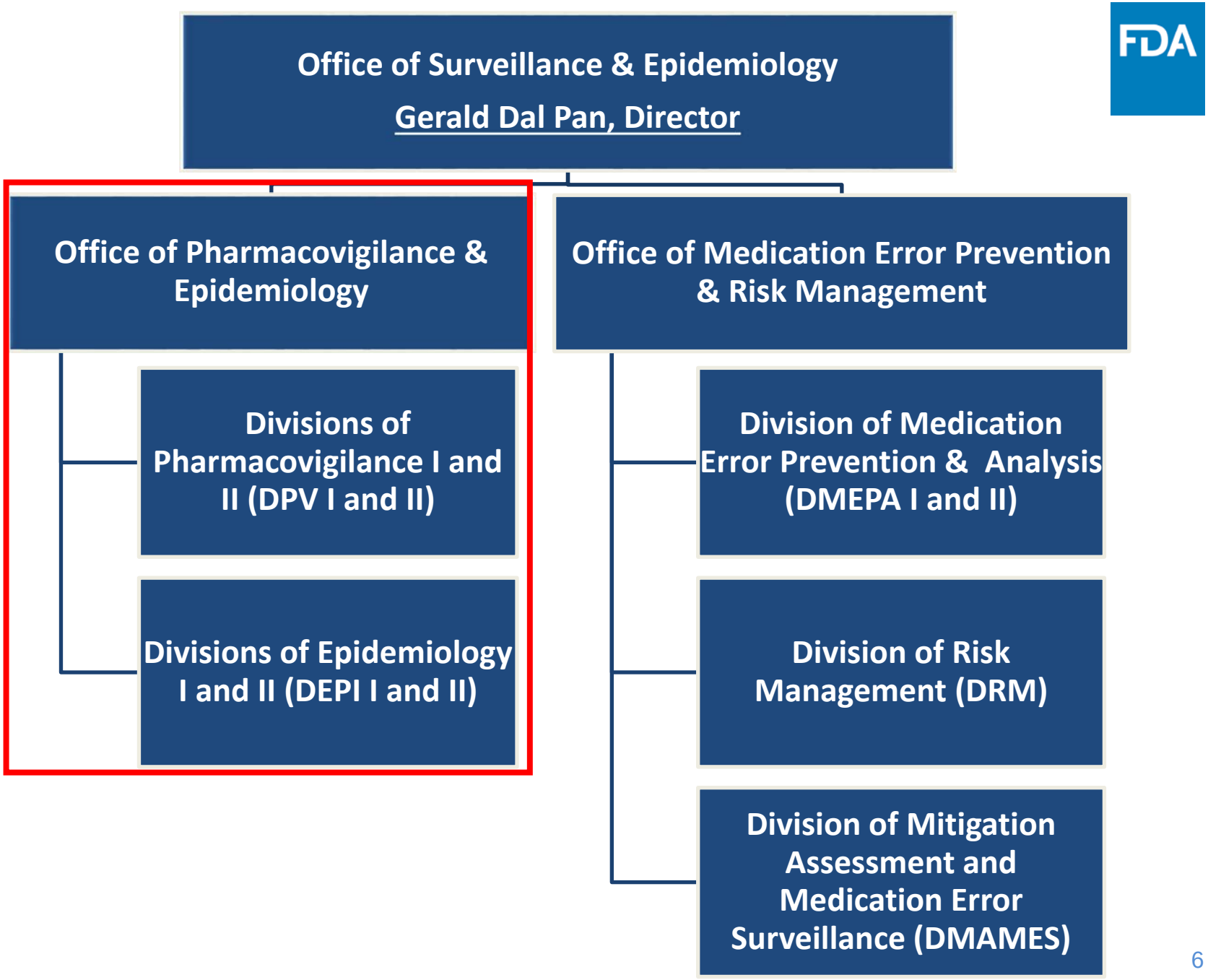
Office of Compliance

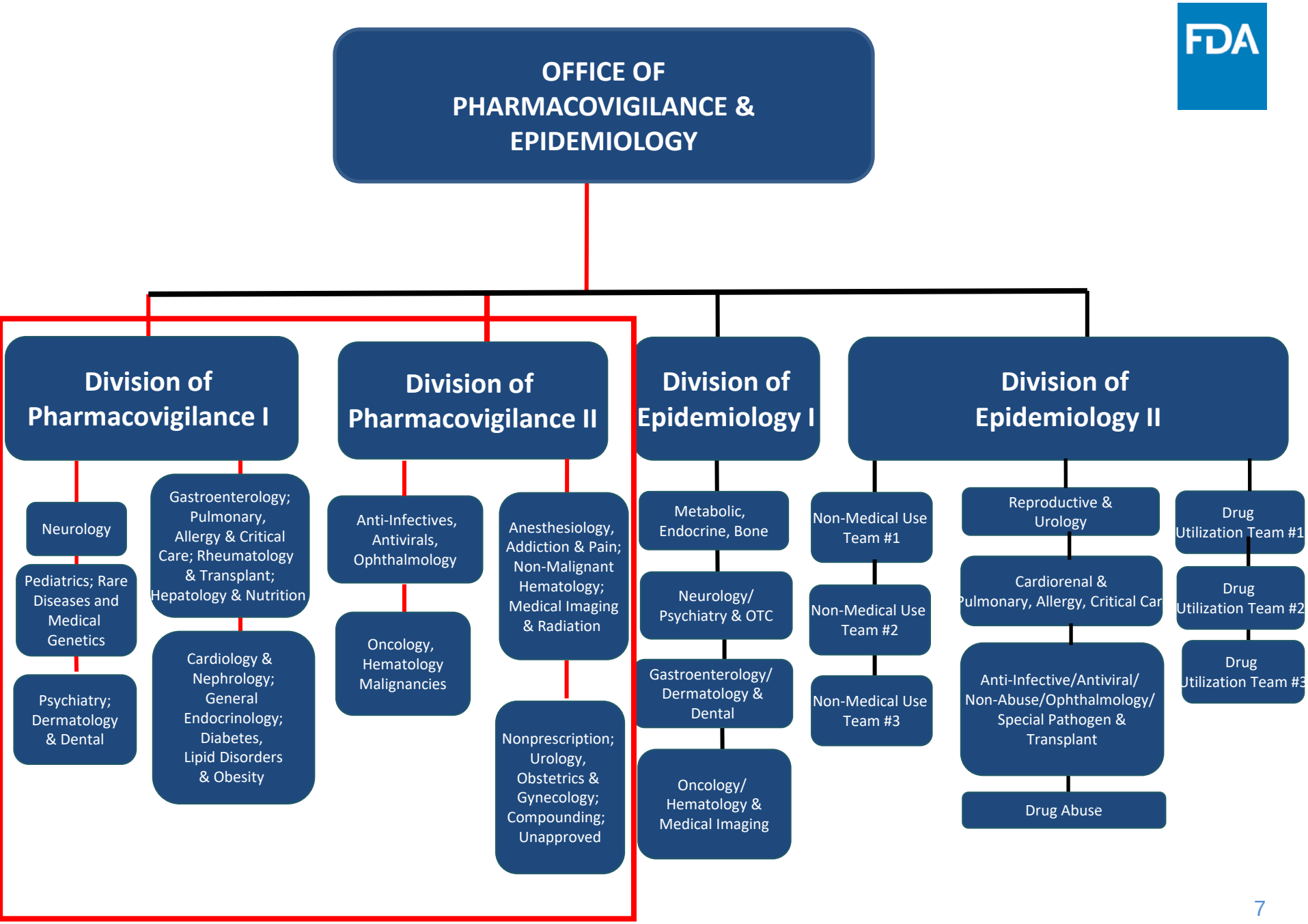
Office of New Drugs

Office of Generic Drugs

Office of Pharmaceutical Quality

Office of Surveillance and Epidemiology


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 I and II)
Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)


OFFICE OF PHARMACOVIGILANCE & EPIDEMIOLOGY
Division of Pharmacovigilance I
Neurology
Pediatrics; Rare Diseases and Medical Genetics
Psychiatry; Dermatology & Dental
Gastroenterology; Pulmonary, Allergy & Critical Care; Rheumatology & Transplant; Hepatology & Nutrition
Cardiology & Nephrology; General Endocrinology; Diabetes, Lipid Disorders & Obesity
Division of Pharmacovigilance II
Anti-Infectives, Antivirals, Ophthalmology
Oncology, Hematology Malignancies
Anesthesiology, Addiction & Pain; Non-Malignant Hematology; Medical Imaging & Radiation
Nonprescription; Urology, Obstetrics & Gynecology; Compounding; Unapproved
Division of Epidemiology I
Metabolic, Endocrine, Bone
Neurology/ Psychiatry & OTC
Gastroenterology/ Dermatology & Dental
Oncology/ Hematology & Medical Imaging
Division of Epidemiology II
Non-Medical Use Team #1
Non-Medical Use Team #2
Non-Medical Use Team #3
Reproductive & Urology
Cardiorenal & Pulmonary, Allergy, Critical Car
Anti-Infective/Antiviral/ Non-Abuse/Ophthalmology/ Special Pathogen & Transplant
Drug Abuse
Drug Utilization Team #1
Drug Utilization Team #2
Drug Utilization 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.

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 experts (e.g., DEPI, DMEPA, DRM)
- Recommend regulatory actions
- Communicate relevant safety information

Why does DPV exist?

JAMA | Original Investigation

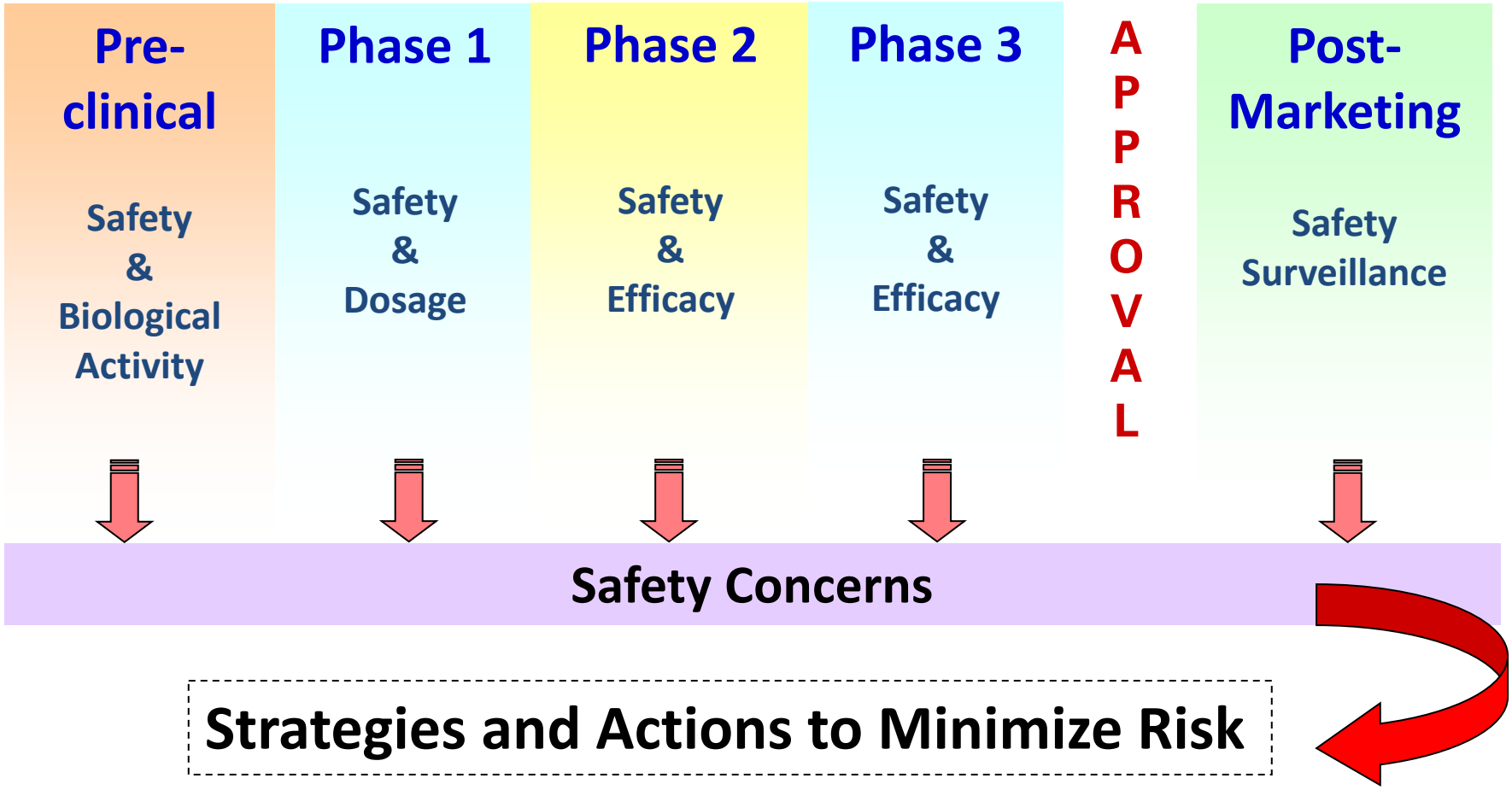
Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

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

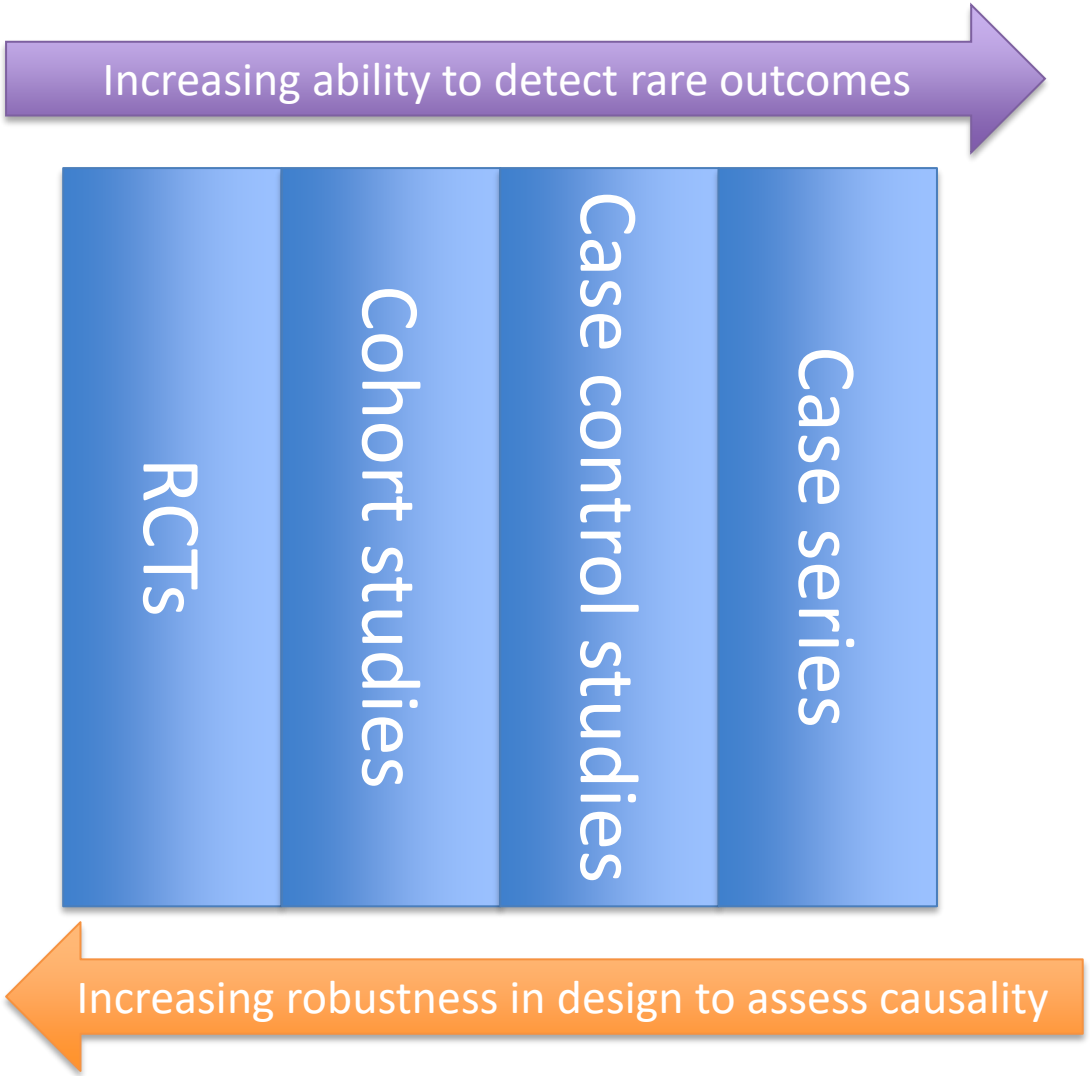
Singh S et al. Trials. 2012;13:138
Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell.

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)

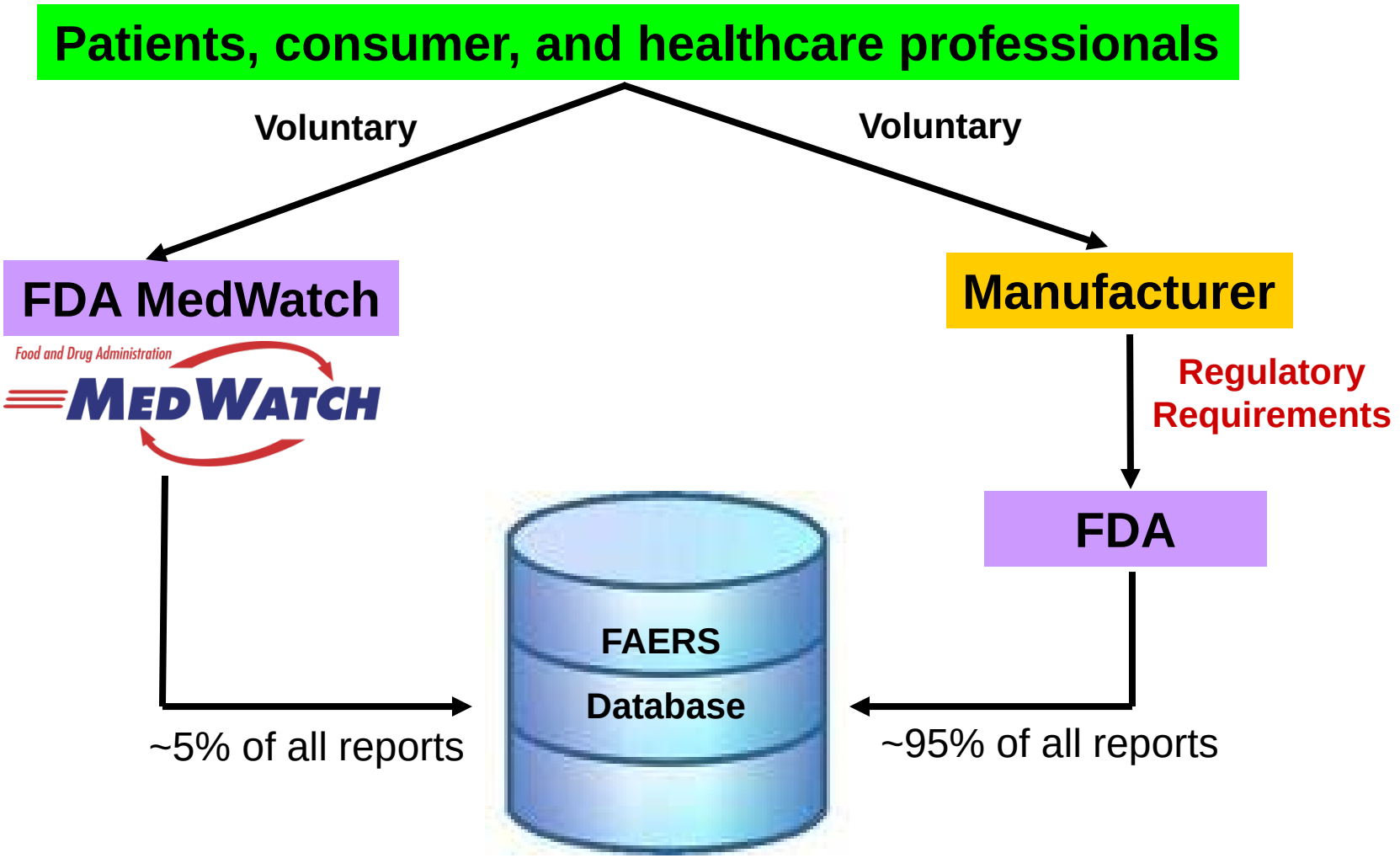
Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell

Strength of Evidence



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 15-day reporting
  - **Non-expedited reports**: Domestic spontaneous adverse events that are:
    - Serious and expected
    - Non-serious and unexpected
    - Non-serious and expected
    - Periodic reporting: 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

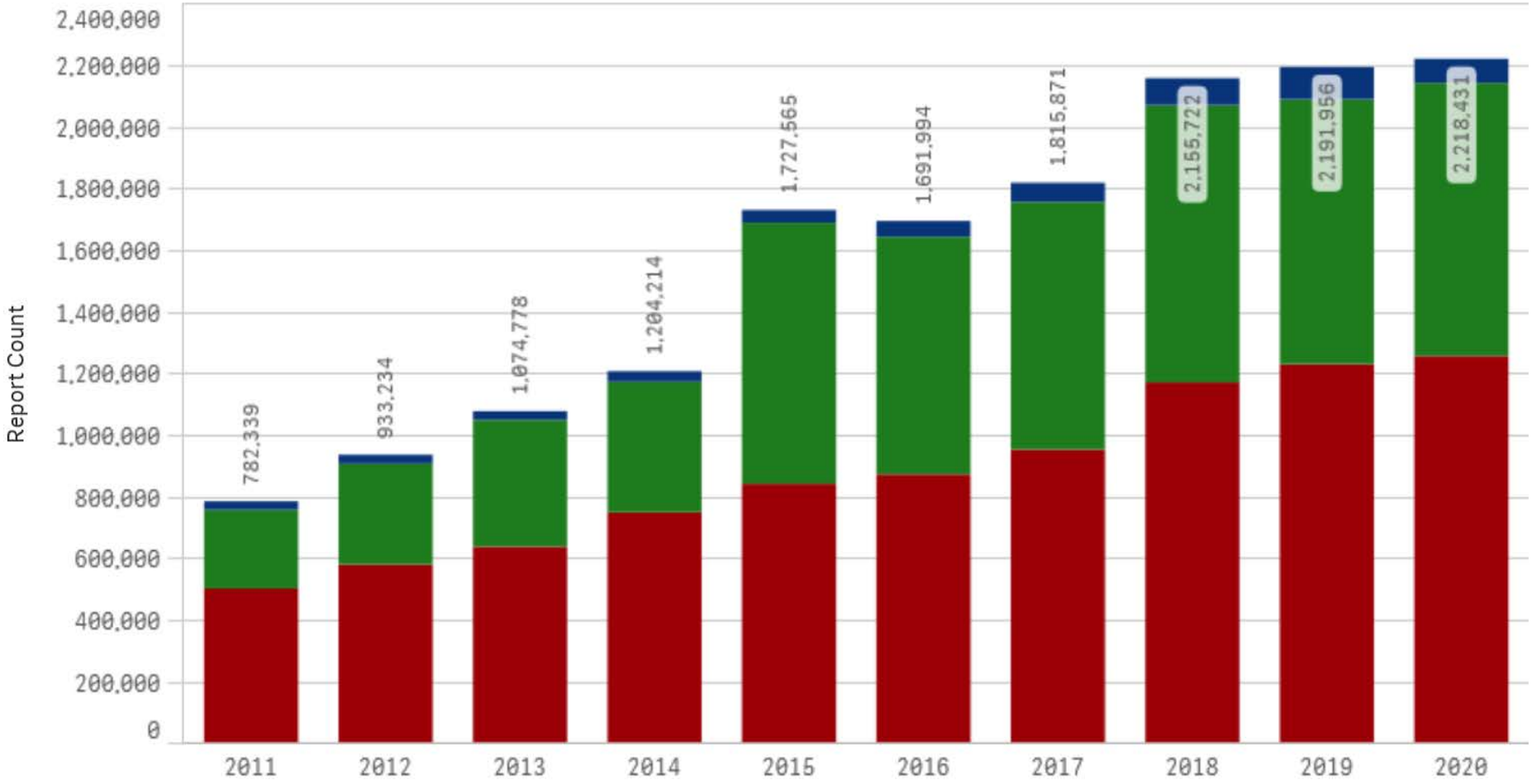
- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event
- Type of drug product and new indications
- Length of time on market
- Extent and quality of manufacturer's surveillance system
- Reporting regulations

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, 2020:
  - 21,416,139 reports received since 1968
- Over 2.22 million new reports received in 2020

Number of Adverse Event Reports Entered into FAERS by Report Type



Data as of December 31, 2020

FAERS Public Dashboard

- Interactive web-based tool for querying FAERS data
- Freedom of Information Act (FOIA) 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

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
- Cannot estimate incidence (underreporting)
- Adverse events that could also be manifestations of the disease for which the drug is indicated
- Dependent on report quality

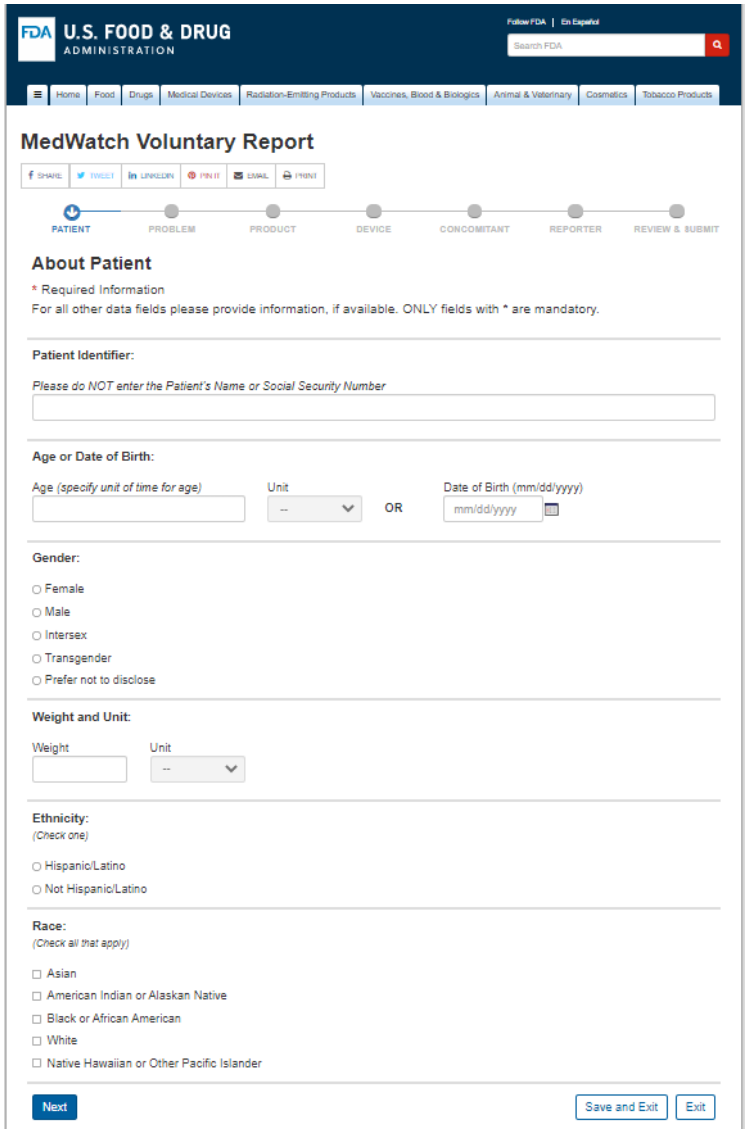
Strom, Brian L; Kimmel, Stephen E; Hennessy, Sean. (2012). Pharmacoepidemiology. Hoboken, NJ: Wiley-Blackwell

How to report to MedWatch

Food and Drug Administration

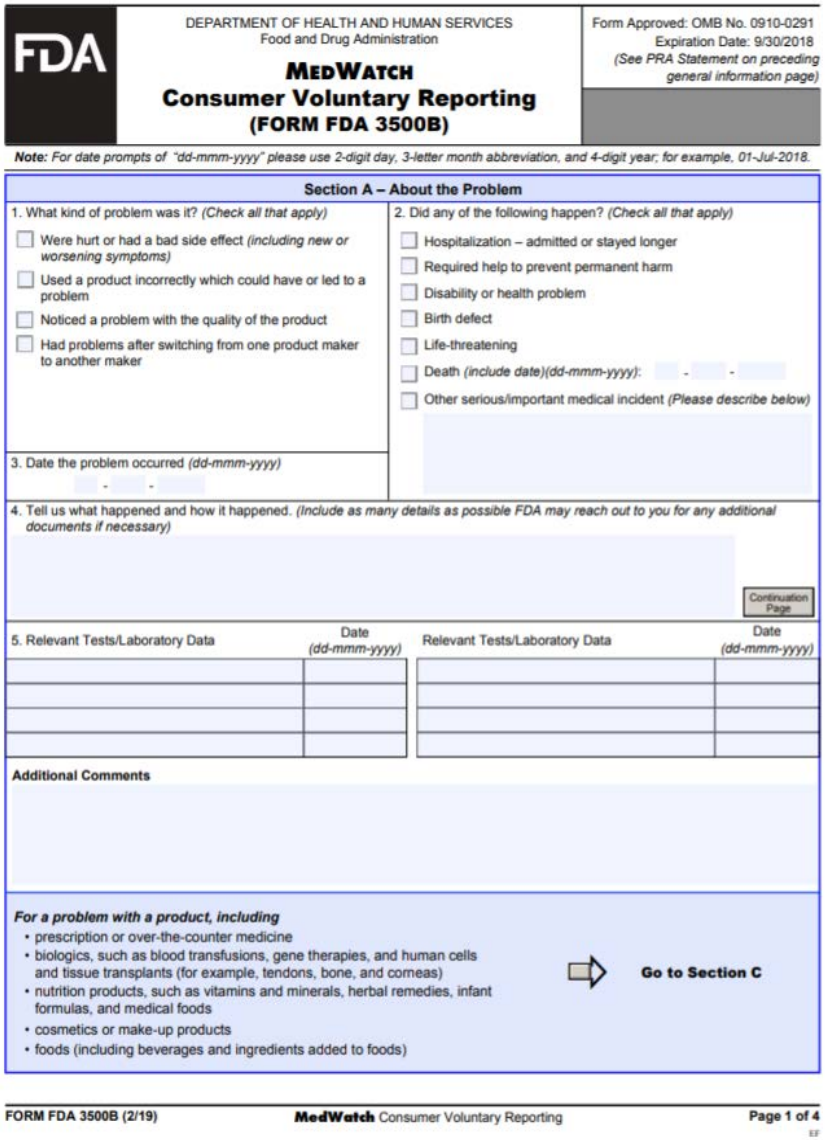
MEDWATCH

- 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

MEDWATCH
Consumer Voluntary Reporting
(FORM FDA 3500B)

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

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-2018.*

Section A – About the Problem

1. 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

2. Did any of the following happen? *(Check all that apply)*
- ☐ Hospitalization – admitted or stayed longer
- ☐ Required help to prevent permanent harm
- ☐ Disability or health problem
- ☐ Birth defect
- ☐ Life-threatening
- ☐ Death *(include date)(dd-mmm-yyyy):* - -
- ☐ Other serious/important medical incident *(Please describe below)*

3. Date the problem occurred *(dd-mmm-yyyy)* - -

4. Tell us what happened and how it happened. *(Include as many details as possible FDA may reach out to you for any additional documents if necessary)*

Continuation Page

5. Relevant Tests/Laboratory Data	Date *(dd-mmm-yyyy)*	Relevant Tests/Laboratory Data	Date *(dd-mmm-yyyy)*

Additional Comments

For a problem with a product, including
- prescription or over-the-counter medicine
- biologics, such as blood transfusions, gene therapies, and human cells and tissue transplants (for example, tendons, bone, and corneas)
- 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 C

FORM FDA 3500B (2/19) **MedWatch** Consumer Voluntary Reporting Page 1 of 4

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 male patient started Drug X at 500 mg daily for cellulitis on April 5, 2018. On an unknown date, the patient developed thrombocytopenia; additional information was not provided.

Case #2: Best Case Representative

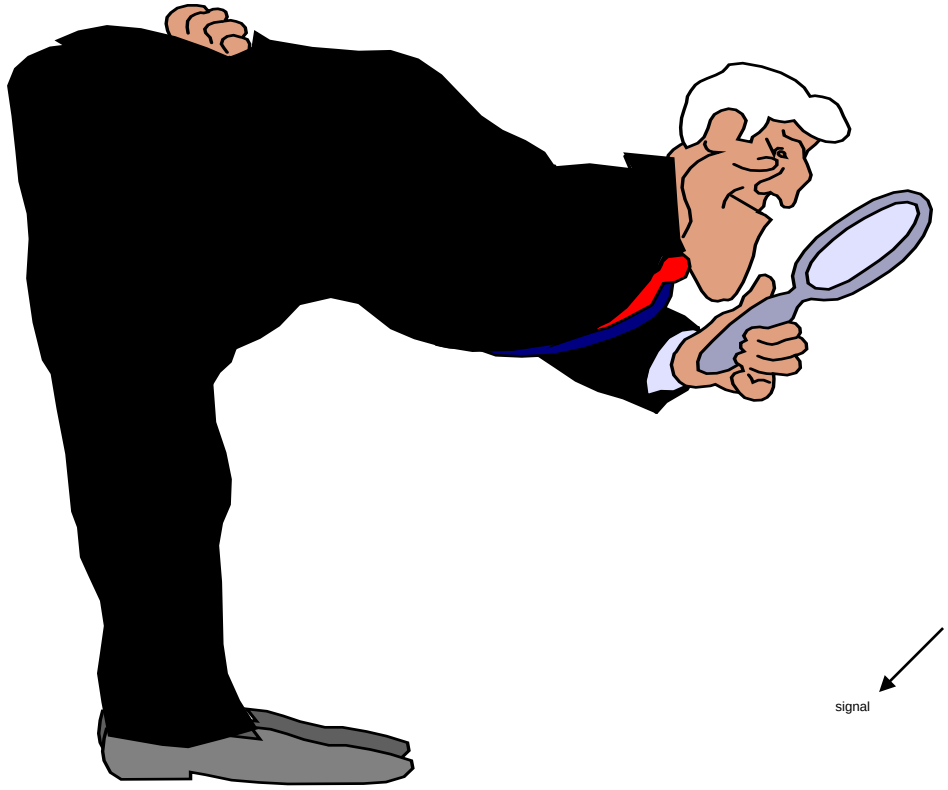
- 60-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of thrombocytopenia.
- Drug X at 500 mg daily on April 5, 2018 for left leg cellulitis.
- Other medications: regular insulin, glyburide, atorvastatin, and lisinopril
- Labs drawn on April 5th revealed all values including platelets were within normal limits.
- 14 days after starting Drug X patient presented to the ER with petechiae, bruising, hematoma and epistaxis.
- Labs on admission: Platelets of 7 x 10^3 /mm^3 (normal range 150 to 450 x10^3 /mm^3)
- He was admitted to ICU and subsequently diagnosed with thrombocytopenia.
- 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?

- 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

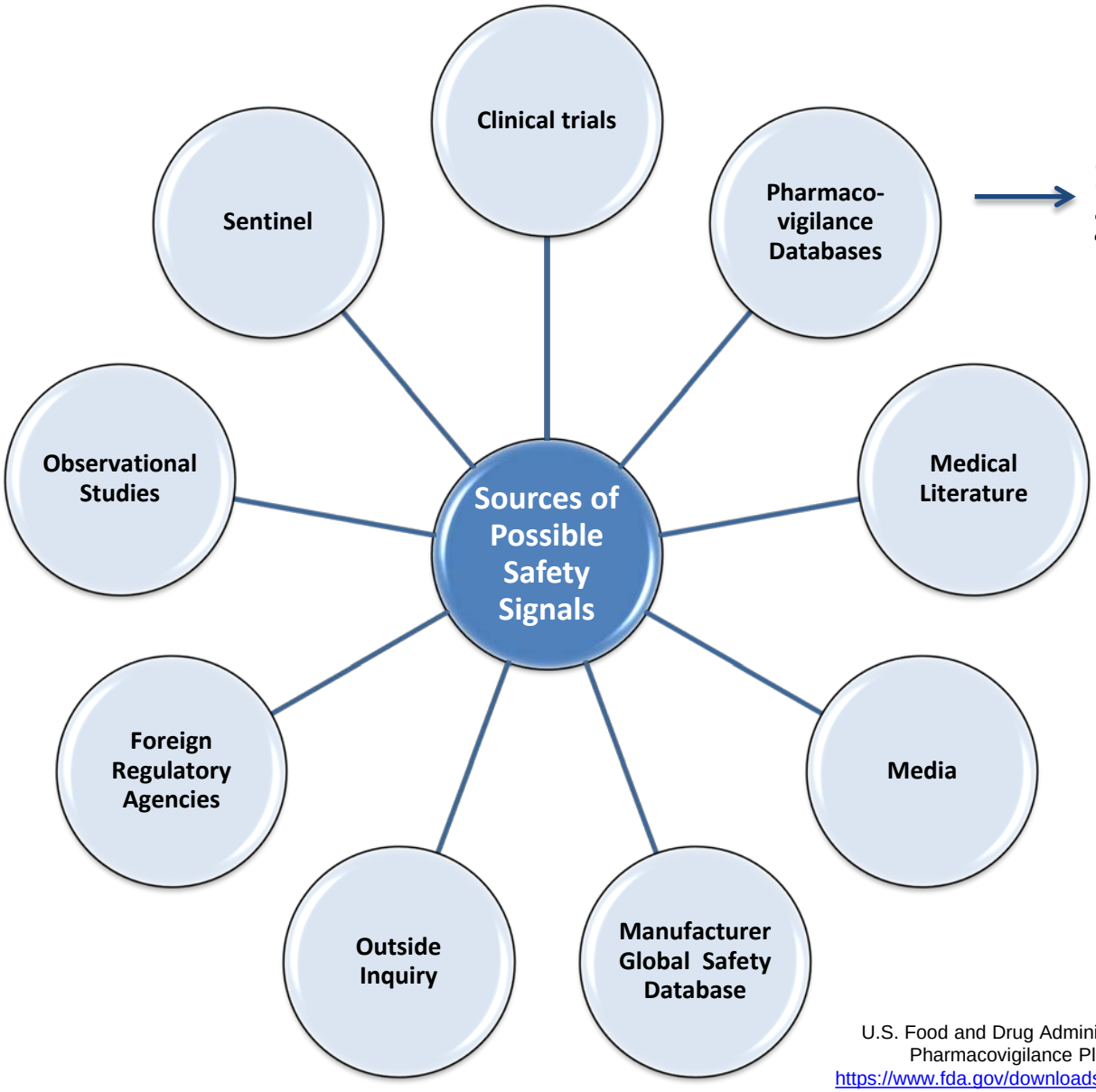
U.S. Food and Drug Administration. Guidance for Industry – E2E Pharmacovigilance Planning, April 2005. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

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



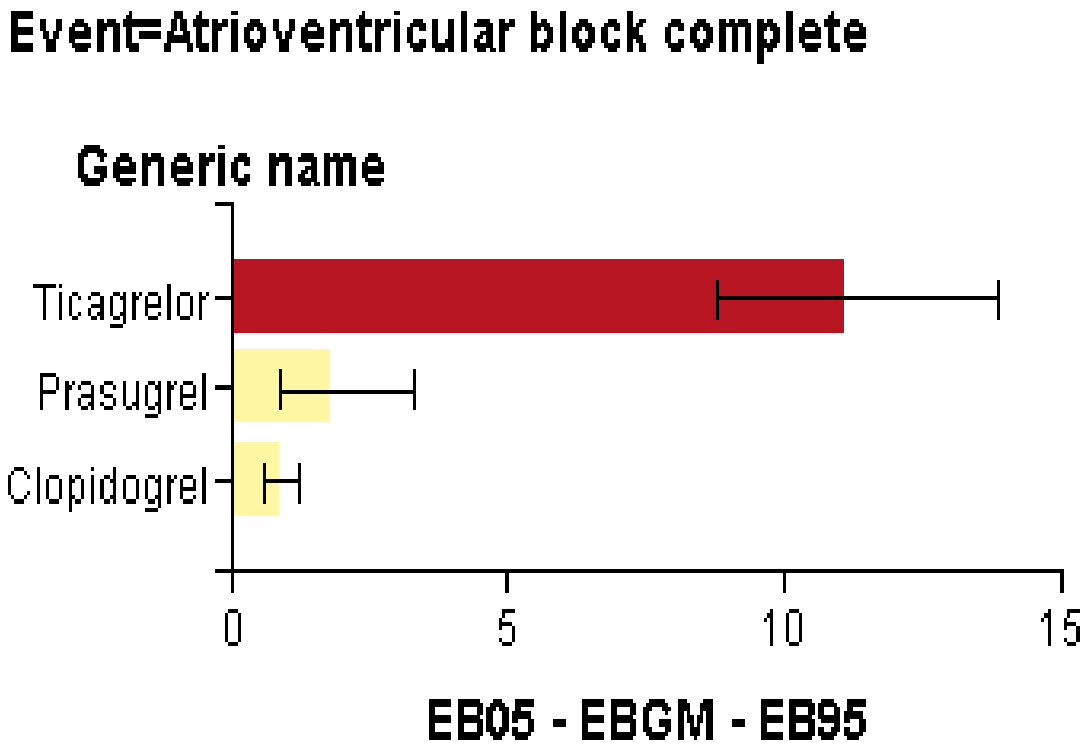
1. FAERS
2. Empirica Signal

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

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)

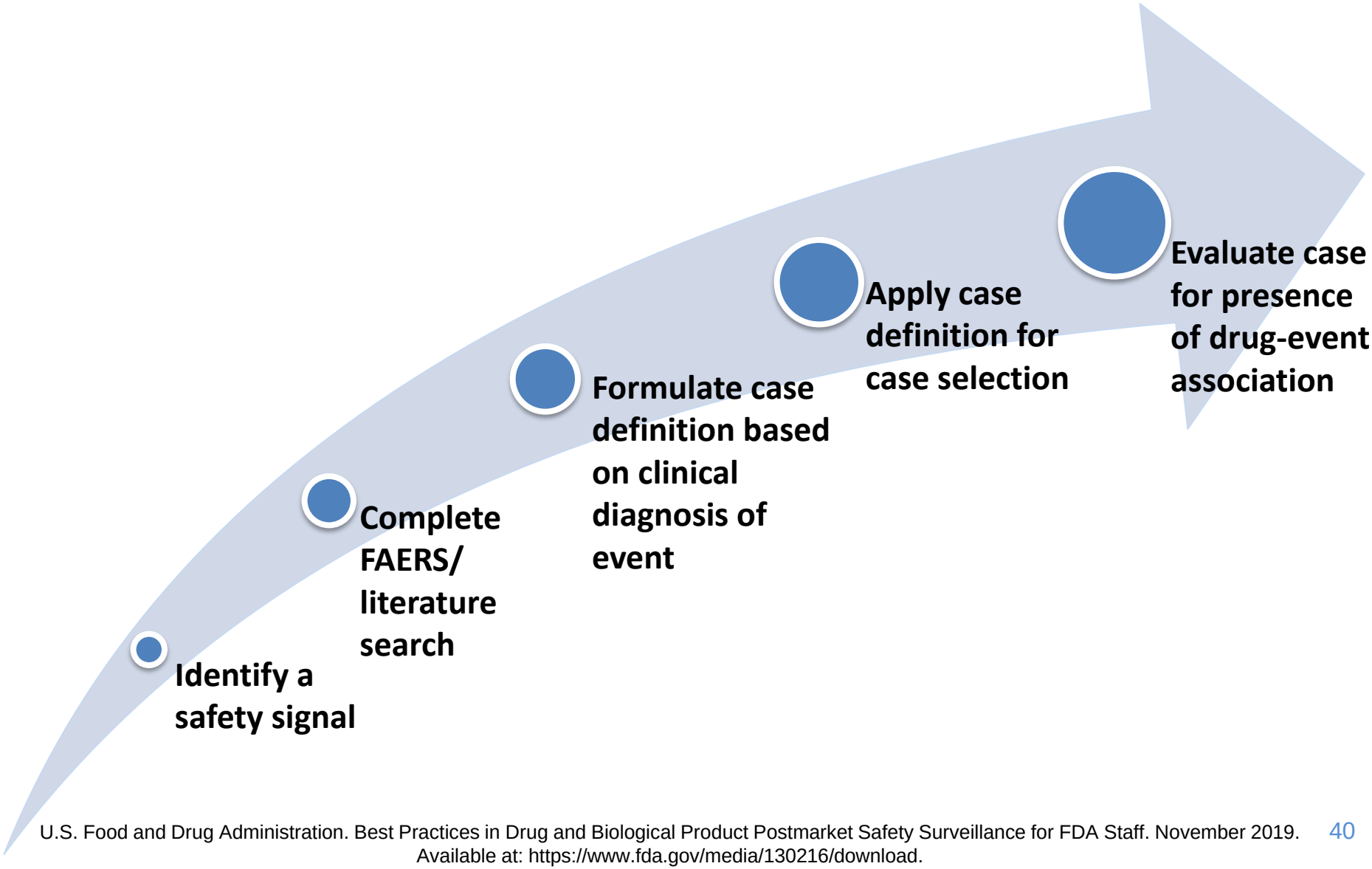
Data Mining Example



Adapted from Empirica Signal

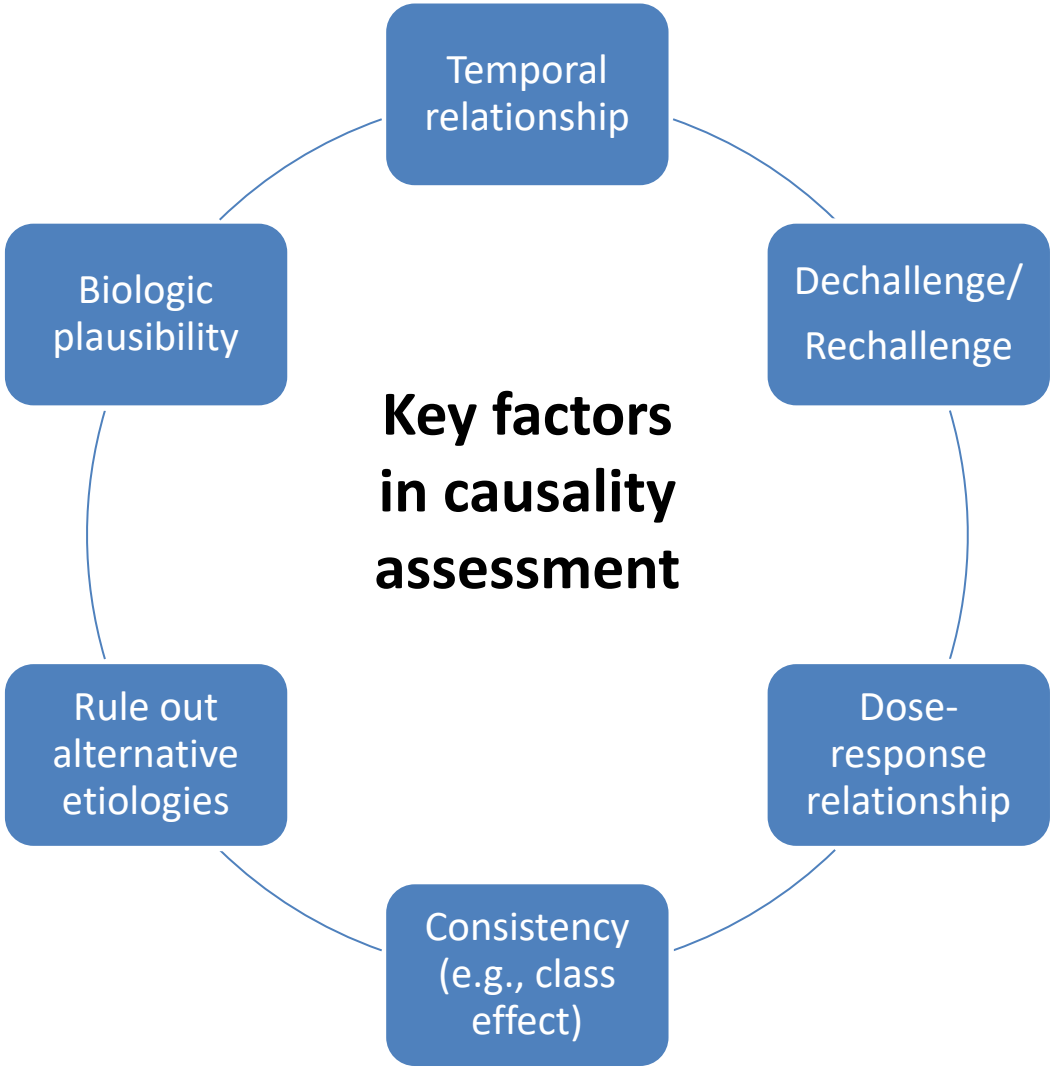
Case Series Development and Evaluation

Developing a Case Series



U.S. Food and Drug Administration. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. Available at: https://www.fda.gov/media/130216/download.

Causality Assessment

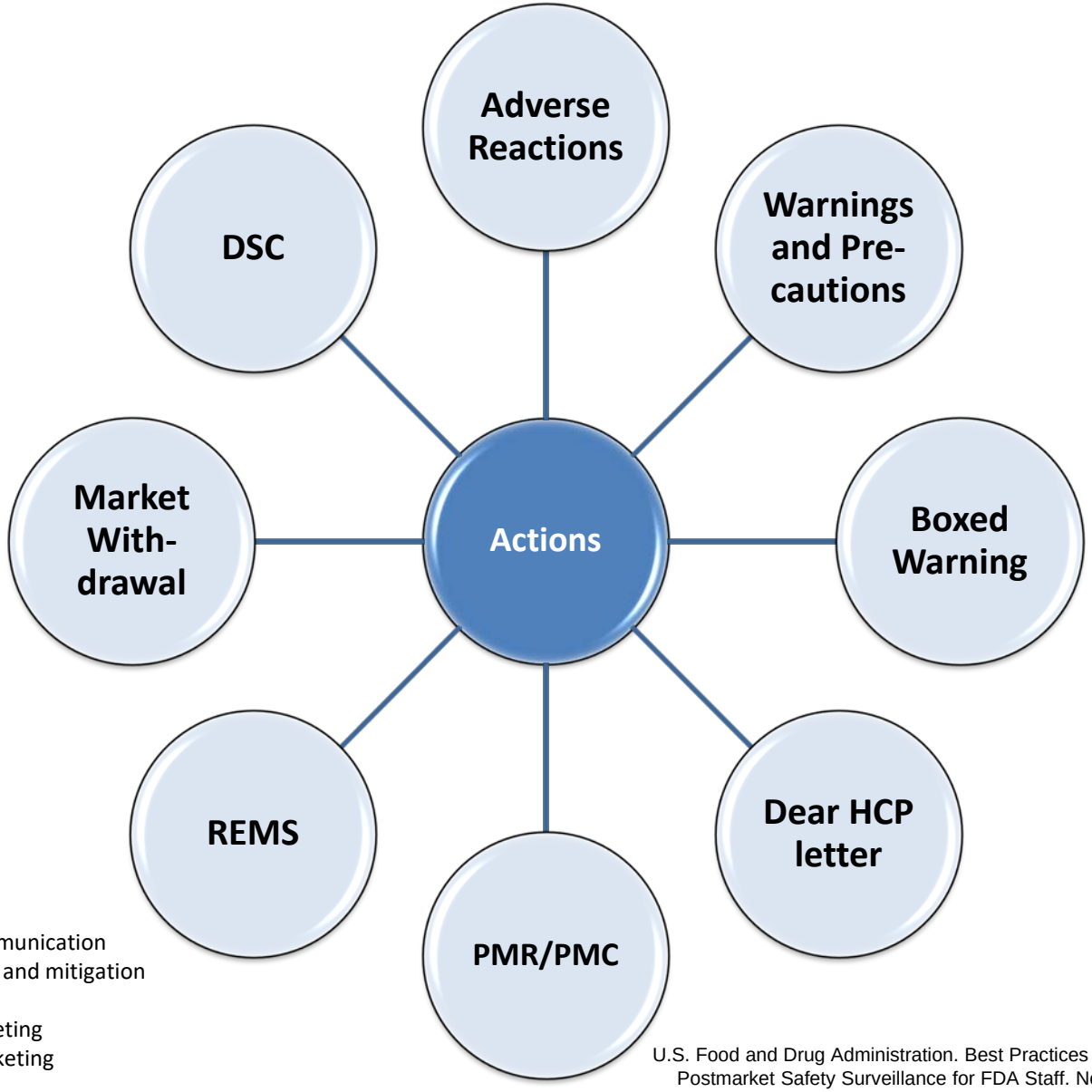


Fedak KM, et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015;12:14.

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
    - Evaluating patient use and labeling
- 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. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. Available at: https://www.fda.gov/media/130216/download.

Communication

<u>Within FDA</u>

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

<u>With FDA Stakeholders</u>

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

Communicating Safety Issues to the Public and Scientific Community

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

Recent Safety Issues Investigated by DPV

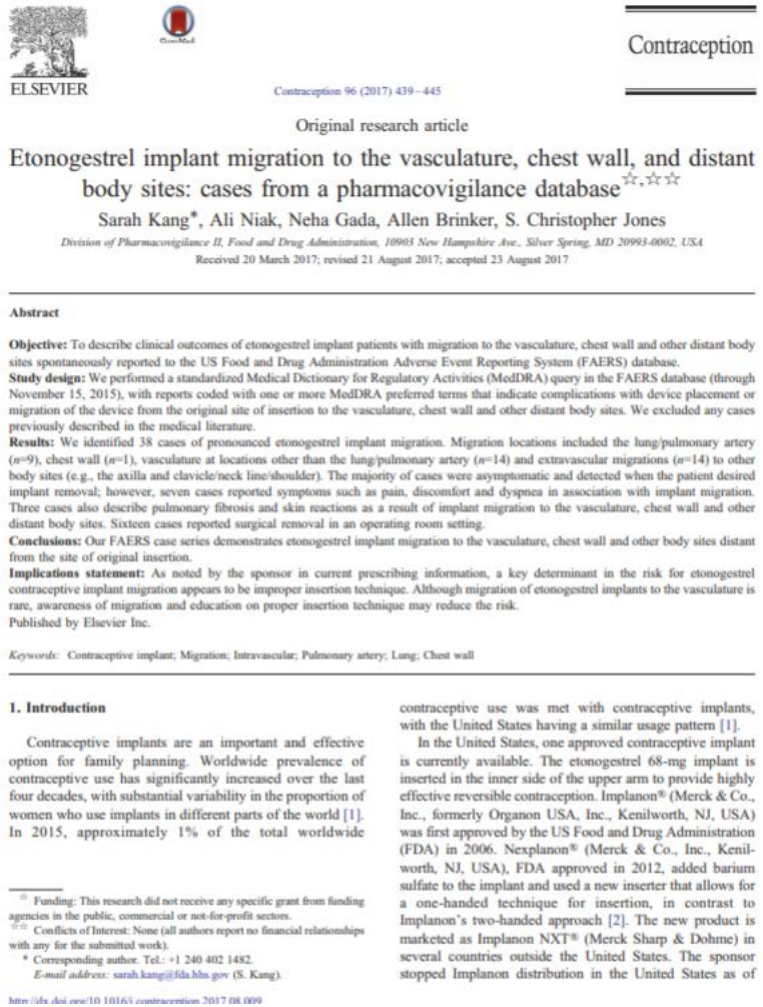
Recent Drug Safety Communications

- 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)
- Constipation caused by schizophrenia medicine clozapine (Clozaril) can lead to serious bowel problems (January 2020)
- Serious liver injury from use of Ocaliva (obeticholic acid) in primary biliary cholangitis patients with advanced cirrhosis (May 2021)
- Vapors from alcohol-based hand sanitizers can have headache, nausea, and dizziness (June 2021)

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
U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that untreated constipation caused by schizophrenia medicine clozapine (Clozaril) can lead to serious bowel problems. (2020). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can
U.S. Food and Drug Administration. FDA Drug Safety Communication: Due to risk of serious liver injury, FDA restricts use of Ocaliva (obeticholic acid) in primary biliary cholangitis (PBC) patients with advanced cirrhosis. (2021). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis
U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that vapors from alcohol-based hand sanitizers can have side effects. (2021). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-vapors-alcohol-based-hand-sanitizers-can-have-side-effects

Safety signal examples

Nexplanon/Implanon Migration



ELSEVIER

Contraception

Contraception 96 (2017) 439–445

Original research article

Etonogestrel implant migration to the vasculature, chest wall, and distant body sites: cases from a pharmacovigilance database☆,☆☆

Sarah Kang*, Ali Niak, Neha Gada, Allen Brinker, S. Christopher Jones

Division of Pharmacovigilance II, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, USA

Received 20 March 2017; revised 21 August 2017; accepted 23 August 2017

Abstract

Objective: To describe clinical outcomes of etonogestrel implant patients with migration to the vasculature, chest wall and other distant body sites spontaneously reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.
Study design: We performed a standardized Medical Dictionary for Regulatory Activities (MedDRA) query in the FAERS database (through November 15, 2015), with reports coded with one or more MedDRA preferred terms that indicate complications with device placement or migration of the device from the original site of insertion to the vasculature, chest wall and other distant body sites. We excluded any cases previously described in the medical literature.
Results: We identified 38 cases of pronounced etonogestrel implant migration. Migration locations included the lung/pulmonary artery (n=9), chest wall (n=1), vasculature at locations other than the lung/pulmonary artery (n=14) and extravascular migrations (n=14) to other body sites (e.g., the axilla and clavicle/neck line/shoulder). The majority of cases were asymptomatic and detected when the patient desired implant removal; however, seven cases reported symptoms such as pain, discomfort and dyspnea in association with implant migration. Three cases also describe pulmonary fibrosis and skin reactions as a result of implant migration to the vasculature, chest wall and other distant body sites. Sixteen cases reported surgical removal in an operating room setting.
Conclusions: Our FAERS case series demonstrates etonogestrel implant migration to the vasculature, chest wall and other body sites distant from the site of original insertion.
Implications statement: As noted by the sponsor in current prescribing information, a key determinant in the risk for etonogestrel contraceptive implant migration appears to be improper insertion technique. Although migration of etonogestrel implants to the vasculature is rare, awareness of migration and education on proper insertion technique may reduce the risk.
Published by Elsevier Inc.

Keywords: Contraceptive implant; Migration; Intravascular; Pulmonary artery; Lung; Chest wall

1. Introduction

Contraceptive implants are an important and effective option for family planning. Worldwide prevalence of contraceptive use has significantly increased over the last four decades, with substantial variability in the proportion of women who use implants in different parts of the world [1]. In 2015, approximately 1% of the total worldwide contraceptive use was met with contraceptive implants, with the United States having a similar usage pattern [1].

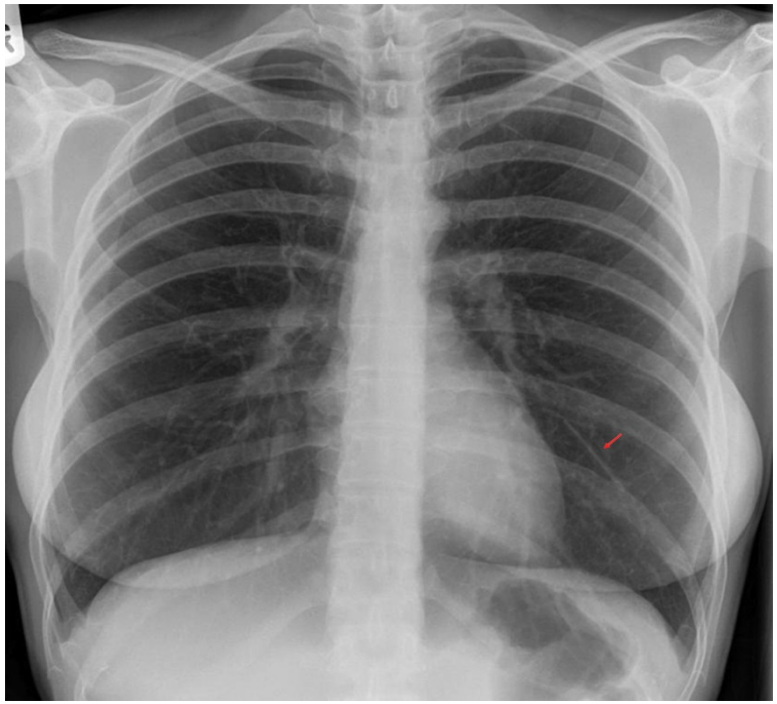
In the United States, one approved contraceptive implant is currently available. The etonogestrel 68-mg implant is inserted in the inner side of the upper arm to provide highly effective reversible contraception. Implanon® (Merck & Co., Inc., formerly Organon USA, Inc., Kenilworth, NJ, USA) was first approved by the US Food and Drug Administration (FDA) in 2006. Nexplanon® (Merck & Co., Inc., Kenilworth, NJ, USA), FDA approved in 2012, added barium sulfate to the implant and used a new inserter that allows for a one-handed technique for insertion, in contrast to Implanon's two-handed approach [2]. The new product is marketed as Implanon NXT® (Merck Sharp & Dohme) in several countries outside the United States. The sponsor stopped Implanon distribution in the United States as of

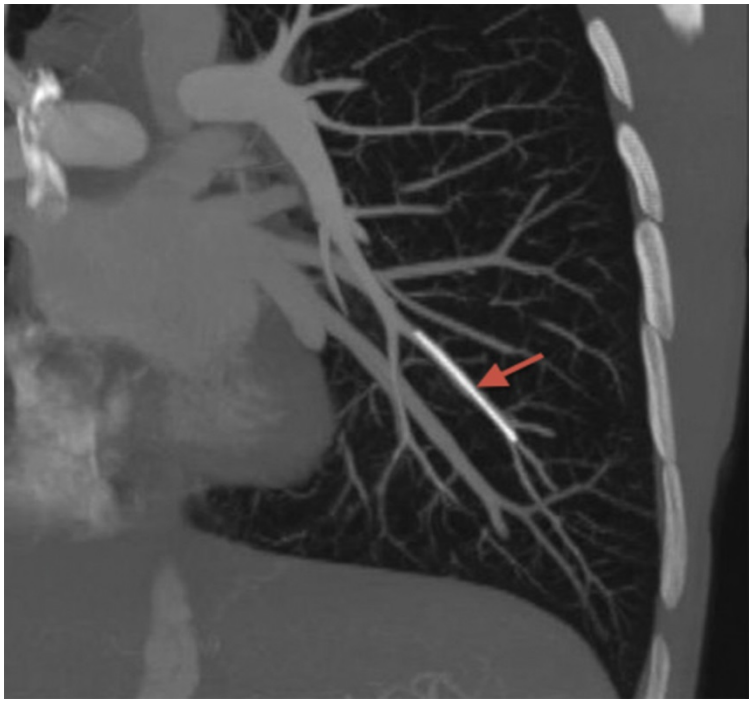
☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.
☆☆ Conflicts of Interest: None (all authors report no financial relationships with any for the submitted work).
* Corresponding author. Tel.: +1 240 402 1482.
E-mail address: sarah.kang@fda.hhs.gov (S. Kang).

http://dx.doi.org/10.1016/j.contraception.2017.08.009

- Migration is a labeled event since Implanon® approval
  - Local migration wording was added in 2008: "There have been occasional reports of migration of the implant; usually this involves minor movement relative to the original position
- FAERS and literature cases of migration of Implanon® and Nexplanon® implants to the vasculature, chest wall, and other parts of body

Nexplanon/Implanon Migration



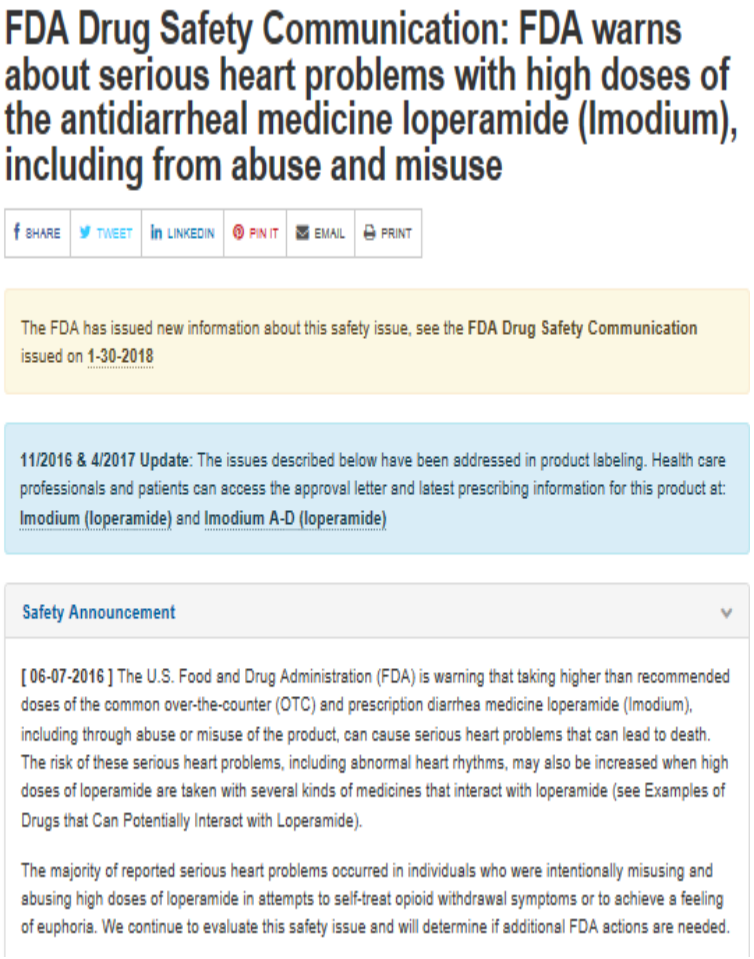


Patel A, D Shetty, N Hollings, and N Dodds. Contraceptive implant embolism into the pulmonary artery. *Ann Thorac Surg* 2014;97:1452.

Regulatory Action

- Labeling supplement approved (March 2016)
  - Instructions for Use: to avoid deep insertion, which can result in difficult localization and removal
  - Localization and removal of a non-palpable implant section
  - Reported migration to pulmonary artery (Warnings and Precautions) and chest wall (Postmarketing Experience)

Loperamide and Cardiac Adverse Events



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

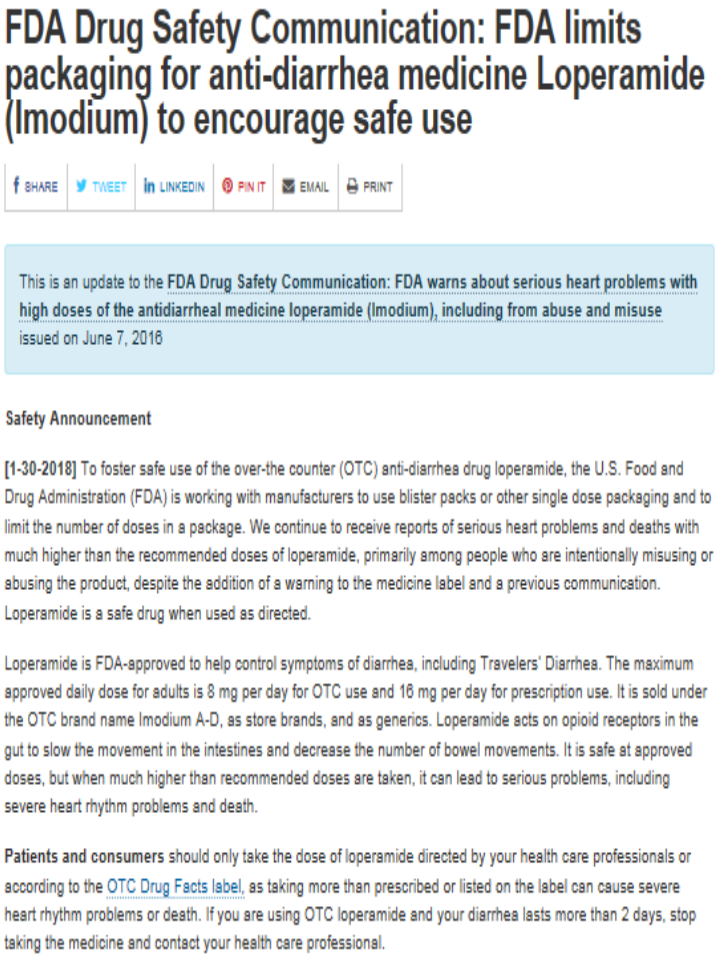
[06-07-2016] The U.S. Food and Drug Administration (FDA) is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead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

- Serious cardiac adverse events, including QT interval prolongation, Torsades de Pointes, and ventricular arrhythmias were reported
- Cases were mostly in individuals taking high doses of loperamide

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 Adverse Events



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.

- Labeling has 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 Adverse Events

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 characte reports of cardiotoxicity, including torsades de pointes (TdP), associated v
Methods: We searched the U.S. Food and Drug Administration Adverse E tem (FAERS) database for post-marketing reports of serious cardiac adver with loperamide use from December 28, 1976 (U.S. drug approval date), th 2015. We also conducted a Pubmed and Google Scholar search to identify reports of cardiotoxicity associated with loperamide in the medical February 11, 2016.
Results: Forty-eight cases of serious cardiac adverse events associated v composed the case series. The most frequently reported cardiac adverse e (n — 24), cardiac arrest (n — 13), QT-interval prolongation (n — 13), ver (n — 10), and TdP (n — 7). There were 10 cases that resulted in death. Of th commonly reported reasons for use can be characterized as drug abuse (r treatment (n — 17). More than one-half of the 48 cases were reported a drug abuse cases, the median daily dose was 250 mg (range 70 mg to 1 occurred as early as 6 hours after a dose and as long as 18 months afte amide. Thirteen of the 22 cases reported using loperamide for euphoric 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.

Lamotrigine and Hemophagocytic Lymphohistocytosis (HLH)

- Lamotrigine is an anti-epileptic indicated for bipolar and epilepsy
- Lamotrigine is associated with immune-related adverse reactions
- HLH is a life-threatening condition in which an antigen trigger produces an excessive immune system activation with resultant immune-mediated pathologic effects
- Clinical manifestations are fever, splenomegaly, and elevated acute phase reactants, ferritin and soluble CD25

Henter J, Horne A, Aricó M, et al. Pediatr Blood Cancer. 2007;48:124–131.

Lamotrigine and Hemophagocytic Lymphohistocytosis (HLH)

- 8 cases reporting hemophagocytic lymphohistocytosis (HLH)
  - 5 Probable cases, 3 Possible cases
- Time to onset: within 24 days
- Treatment: blood products (2), chemotherapy (2), steroids (6), intravenous immune globulin (4)
- Outcomes: Death (1), life-threatening (2), hospitalization (8), other (3)

Regulatory Action

- Recommendation in Warnings and Precautions (8/2018)

5.2 Hemophagocytic Lymphohistocytosis

Hemophagocytic lymphohistocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine extended-release for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Common findings include fever, hepatosplenomegaly, rash lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, hypertriglyceridemia, and liver function and coagulation abnormalities. In cases of HLH reported with lamotrigine extended-release, patients have presented with signs of systemic inflammation (fever, rash, hepatosplenomegaly, and organ system dysfunction) and blood dyscrasias. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. Lamotrigine extended-release should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Drug Safety Communication

FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal)

ARTICLE

Hemophagocytic lymphohistiocytosis associated with the use of lamotrigine

Tiffany Kim, PharmD, Corrinne G. Kulick, PharmD, Cindy M. Kortepeter, PharmD, Allen Brinker, MS, MD, and Peter Waldron, MD

Neurology® 2019;92:e2401-e2405. doi:10.1212/WNL.0000000000007517

Correspondence
Dr. Kim
tiffany.kim@fda.hhs.gov

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

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