# Introduction to Postmarketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER

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Center for Drug Evaluation and Research

# Outline

- FDA organizational structure
- Postmarketing surveillance and FDA Adverse Event Reporting System (FAERS)
- Signal detection
- Case series development and evaluation
- Signal strengthening
- Communicating safety findings

# FDA

Office of the Commissioner

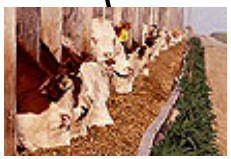
Office of Operations

Office of Foods and Veterinary Medicine

Office of Medical Products and Tobacco

Office of Global Regulatory Operations and Policy

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



**C**enter for **V**eterinary **M**edicine **(CVM)**

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

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

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

**C**enter for **T**obacco **P**roducts **(CTP)**

**O**ffice of **R**egulatory **A**ffairs **(ORA)**

# CDER

Office of Translational Sciences

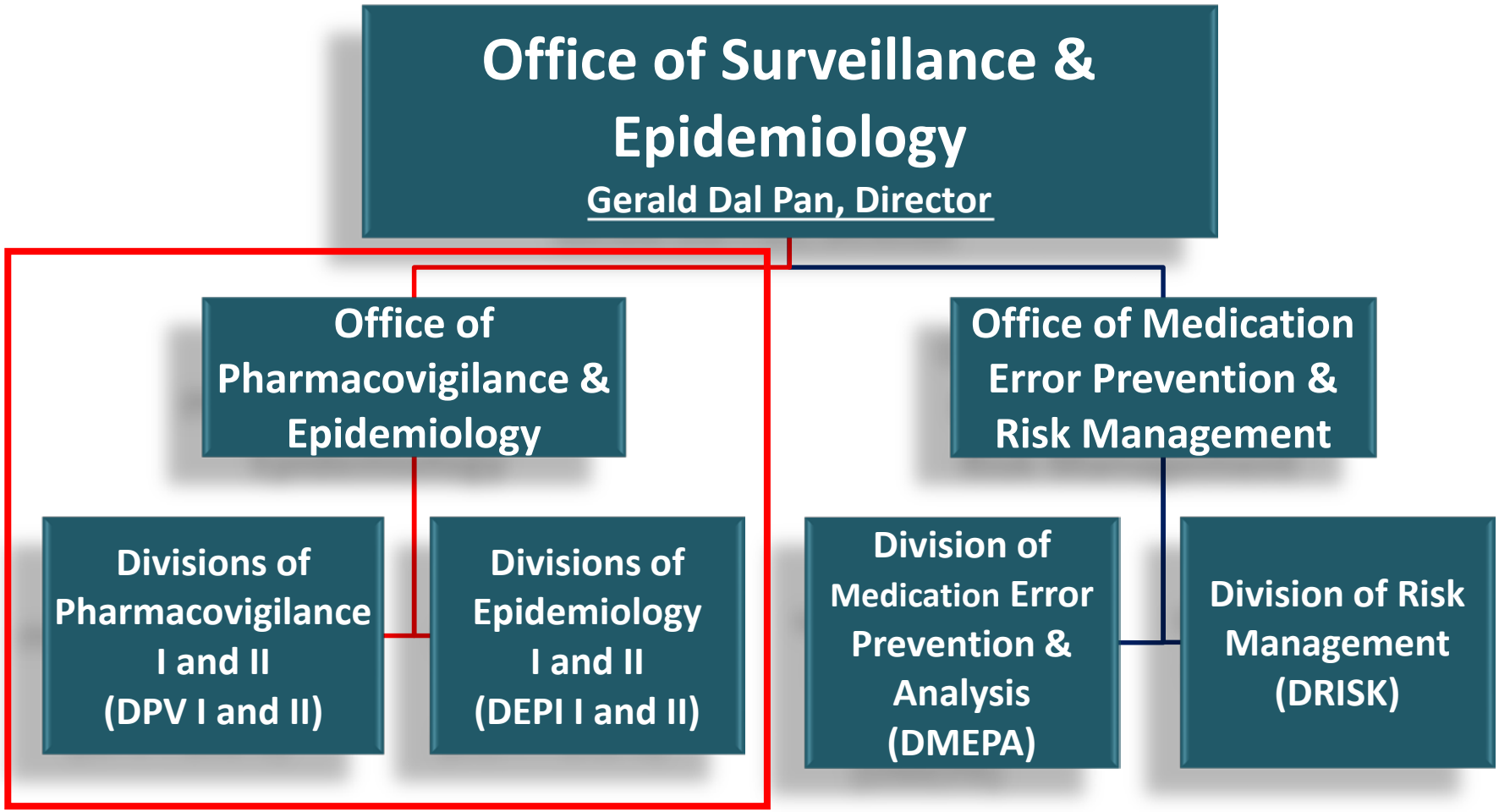
Office of New Drugs

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)

# 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.

# Premarket vs Postmarket Safety Data

| Limitations of Premarket Clinical Trials | Benefits of Postmarket Safety Reporting |
|---|---|
| • Relatively small size of patient population<br>• Narrow population/ indications<br>• Short duration | • Low frequency/rare Adverse Events<br>• Captures adverse events (AEs) from entire population/includes all indications<br>• Drug-drug/food interactions<br>• Detect ↑ severity of known reactions<br>• Direct engagement of healthcare professionals/consumers |

Singh S et al. Trials. 2012;13:138
Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Storm

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

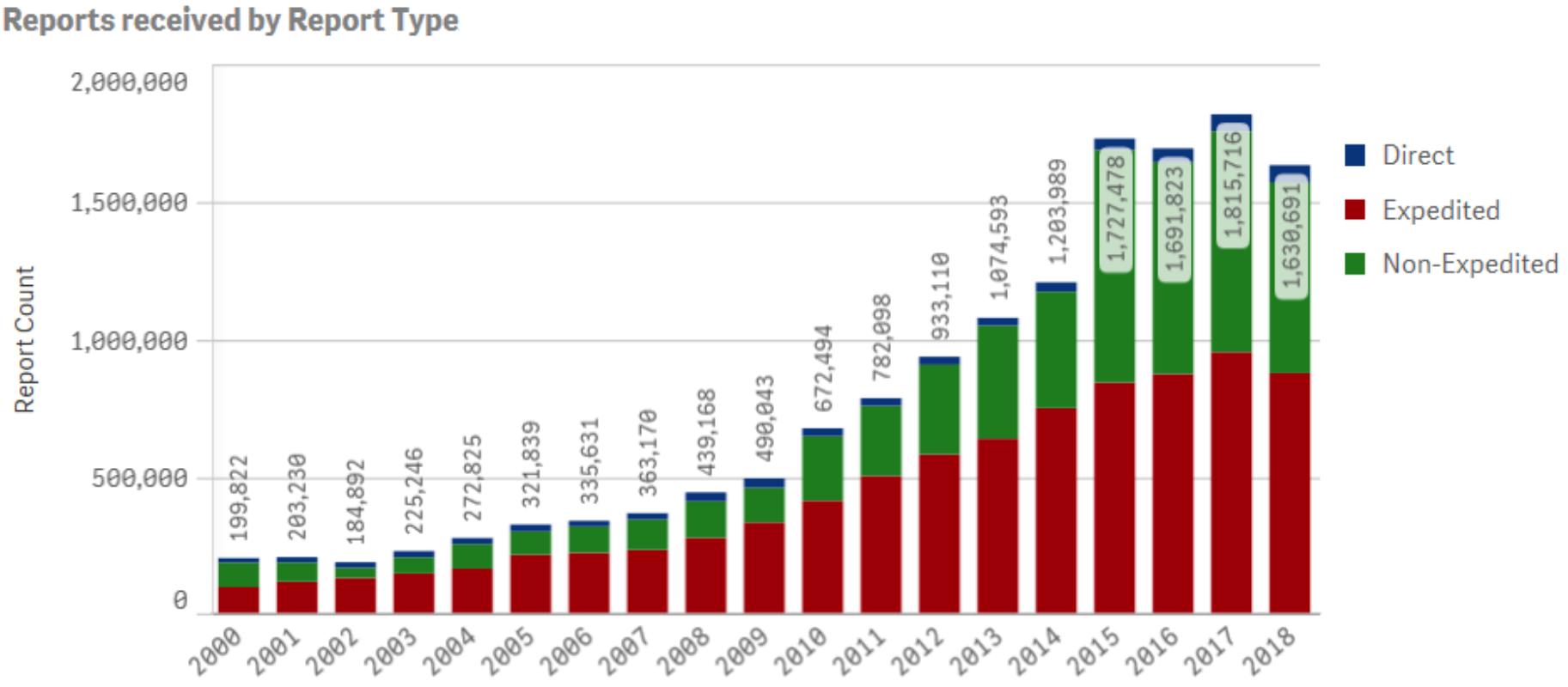
# FDA Adverse Event Reporting System

- 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)*

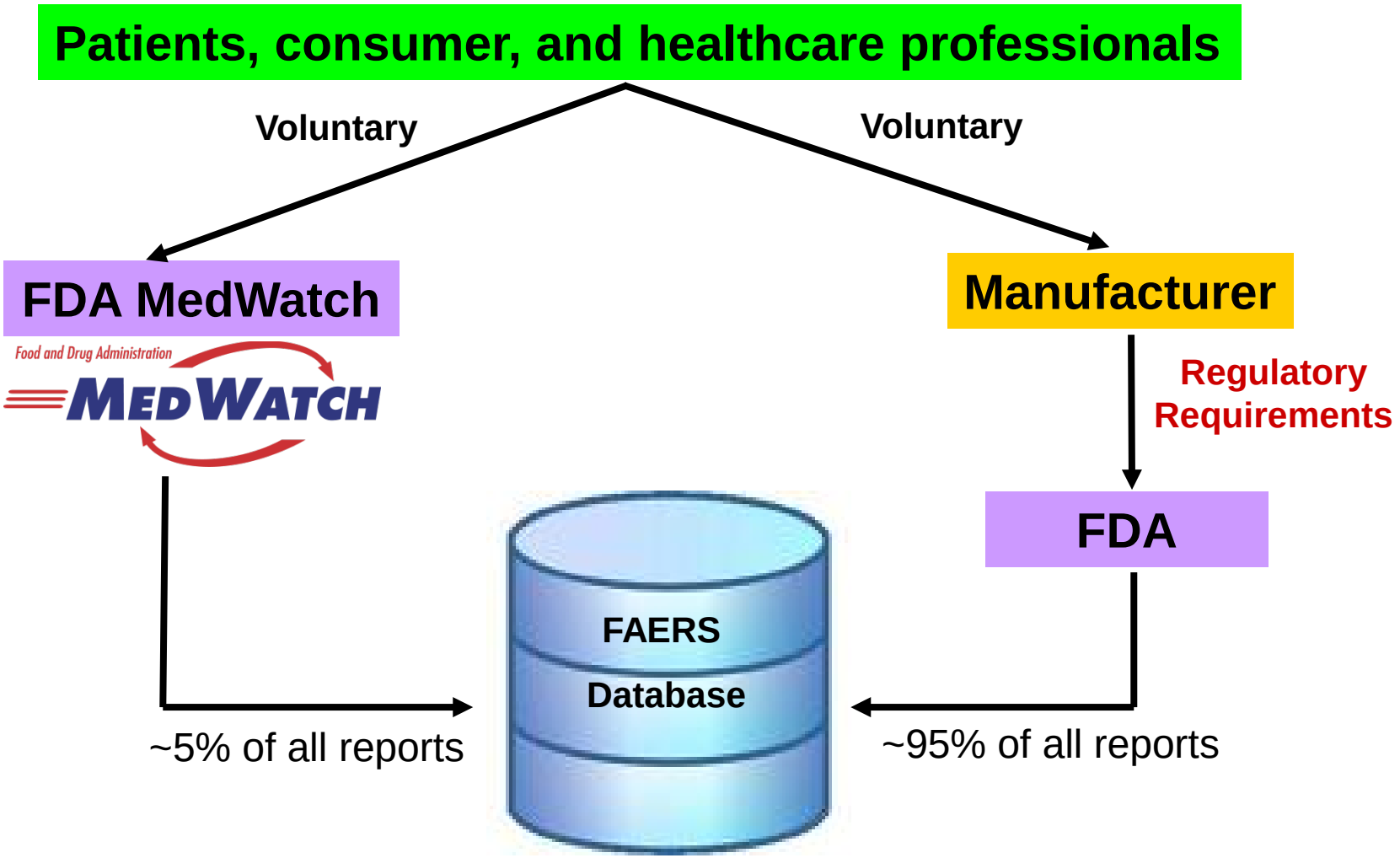
FDA Adverse Event Reporting System

# Number of Adverse Event Reports Entered into FAERS




Data as of September 30, 2018

# How Postmarketing Reports Get to FDA



# Factors Affecting Reporting Trends

- Publicity
  - Media attention
  - Litigation (class action lawsuits)
- Length of time on market
  - Type of drug product
- New indications for an approved drug
- Modifications in a company's reporting requirements
- Changes in reporting regulations

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Strom

# FAERS Strengths and Limitations

**Strengths**

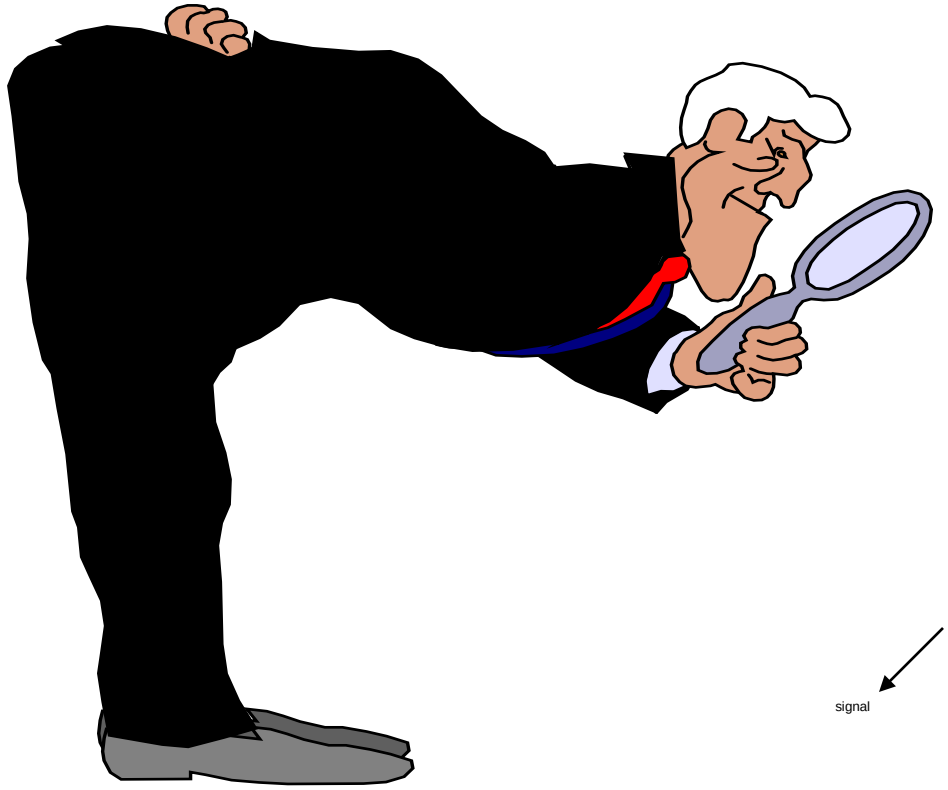
- Includes all marketed products, uses, and patient populations
- Especially good for
  - Rare events
  - Events that occur shortly after exposure

**Limitations**

- Cannot estimate incidence (underreporting)
- Dependent on report quality
- Events that could be manifestations or worsening of the disease for which the drug is indicated
- Events with a long latency

Textbook of Pharmacoepidemiology 5th edition. Edited by Brian Strom

# Safety Signal Detection

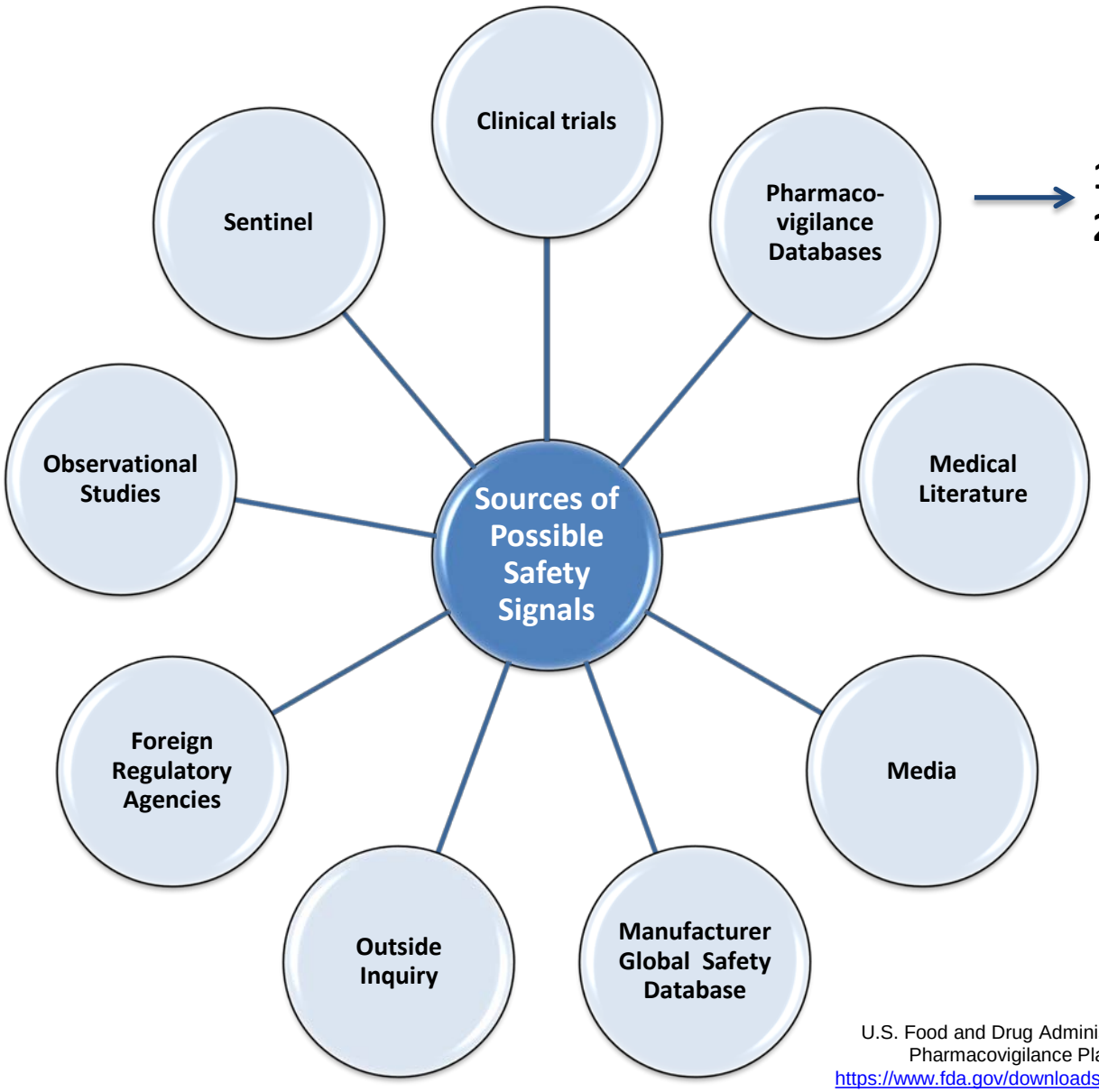


# What is a Safety Signal?

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

# Monitoring FAERS for Safety Signals

- Safety Evaluators are assigned a drug portfolio
- Weekly FAERS "inbox" for newly received reports
- Risk-based principles utilized for report screening

| FAERS Cases By Product Name, Case Type, Outcome | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cases from 14-JAN-2019 to 20-JAN-2019 | | | | | | | | | | | |
| Product Name | Total Cases | Expedited (15-Day) | Direct | Periodic | DE | HO | LT | DS | CA | RI | OT |
| MEFLOQUINE | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Distinct Total Cases** | **1** | **1** | **0** | **0** | **1** | **0** | **0** | **0** | **0** | **0** | **0** |

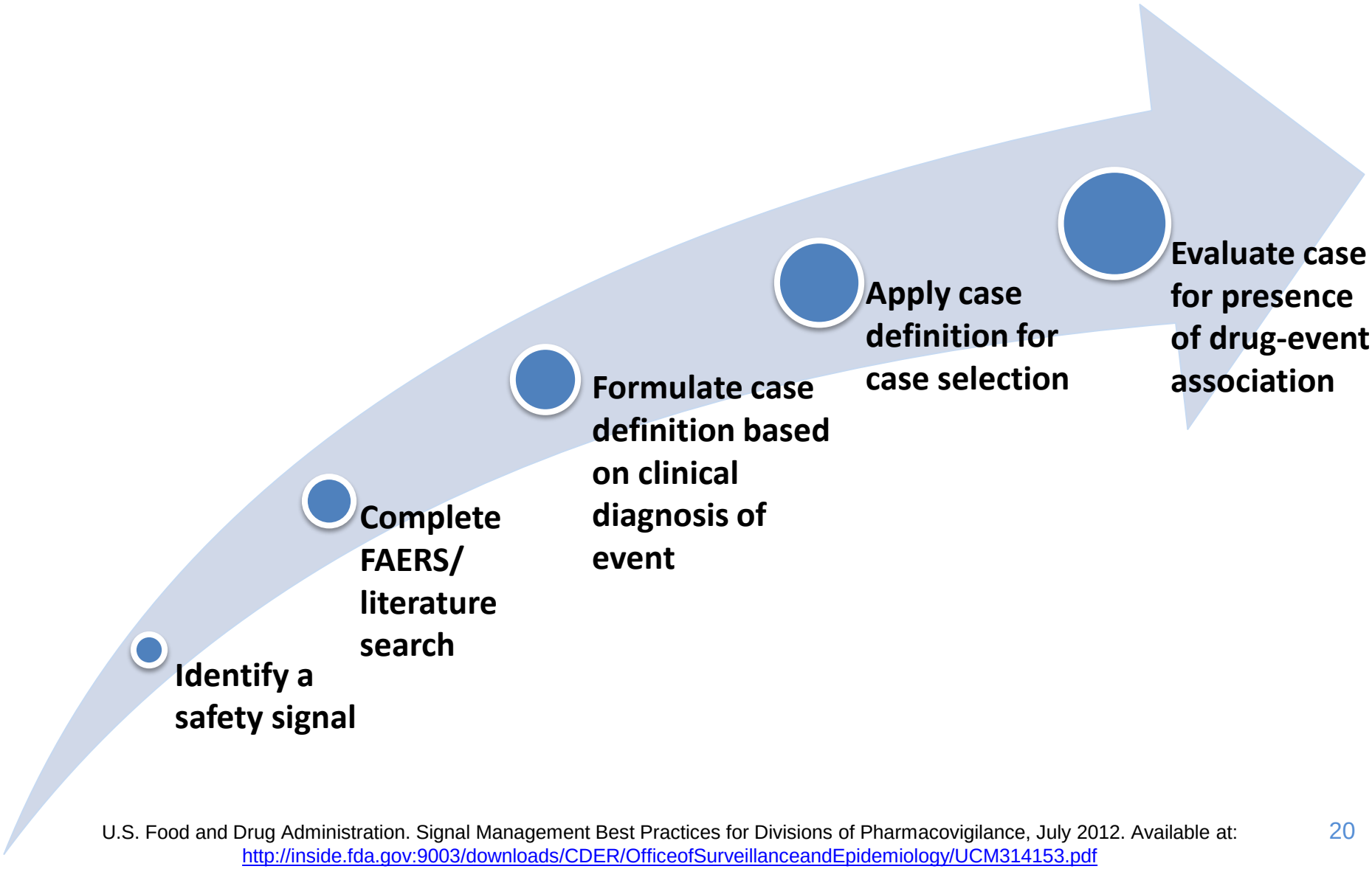
| FAERS Cases by MedDRA Preferred Terms (PT) | | |
|---|---|---|
| Cases from 14-JAN-2019 to 20-JAN-2019 | | |
| MedDRA PTs | Total Cases | Percent of Total |
| ADVERSE EVENT | 1 | 100.00 |
| **Distinct Total Cases** | **1** | **100** |

# Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation; does not prove causation
- Supplements FAERS data review
- Does not replace expert clinical case review

# Case Series Development and Evaluation

# Developing a Case Series



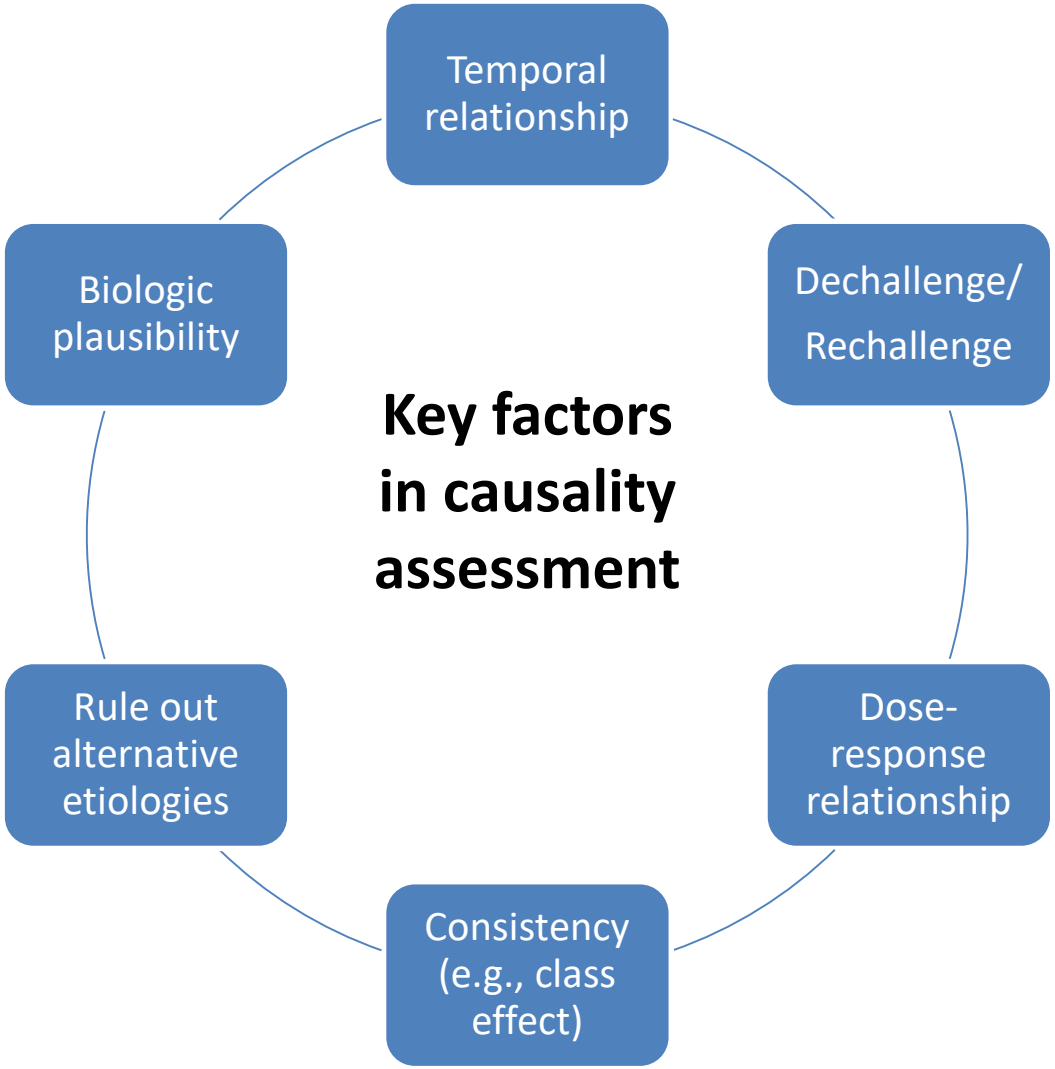

U.S. Food and Drug Administration. Signal Management Best Practices for Divisions of Pharmacovigilance, July 2012. Available at: http://inside.fda.gov:9003/downloads/CDER/OfficeofSurveillanceandEpidemiology/UCM314153.pdf

# 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

# Causality Assessment

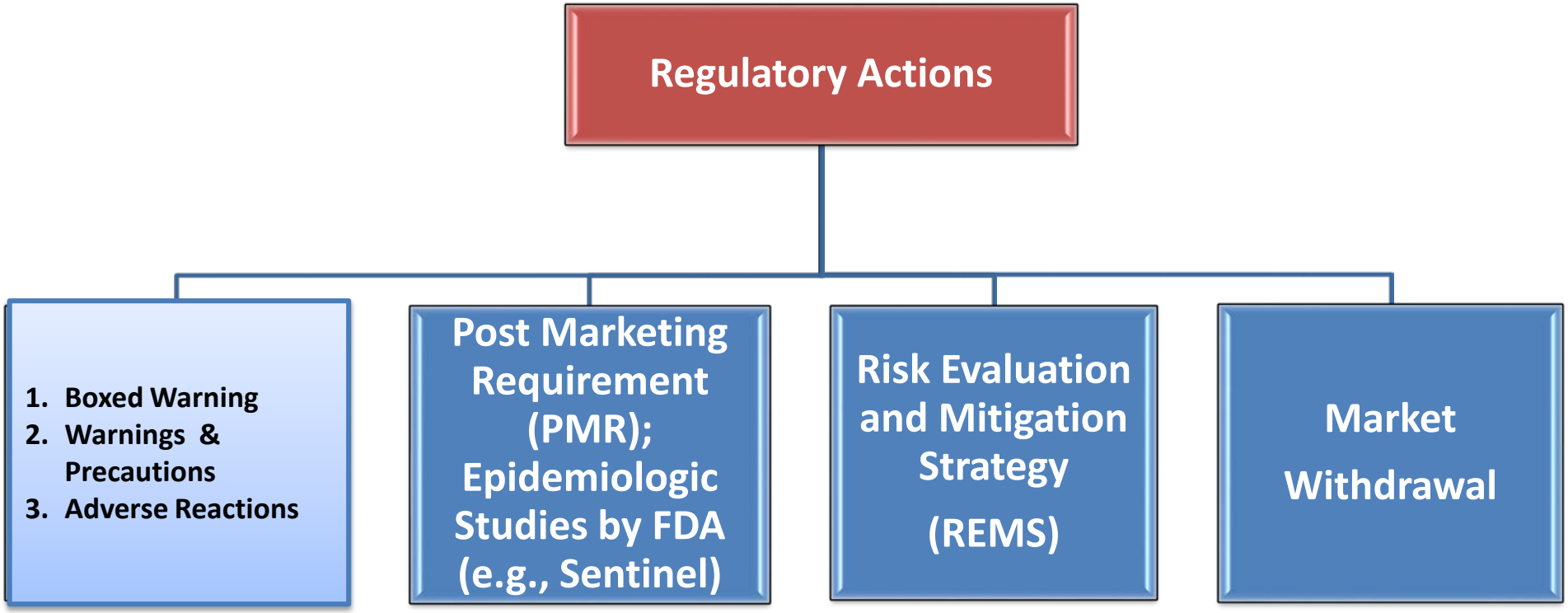



Fedak KM, et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015;12:14.

# Signal Strengthening through Collaboration

- Collaboration within our Office
  - Epidemiology, including Drug Use
    - Evaluate observational studies
    - Quantify a drug-event association
    - Calculate reporting rates
  - Risk Management
    - Develop Risk Evaluation and Mitigation Strategy
- Collaboration outside of our Office within FDA
    - FDA colleagues in other offices
    - Other agencies (e.g., CDC)

# Regulatory Actions and Communication




**Methods of communication:**

1. Drug Safety Communication
2. Publications and scientific meetings
3. Quarterly webposting of new safety information from FAERS (FDAAA 921)

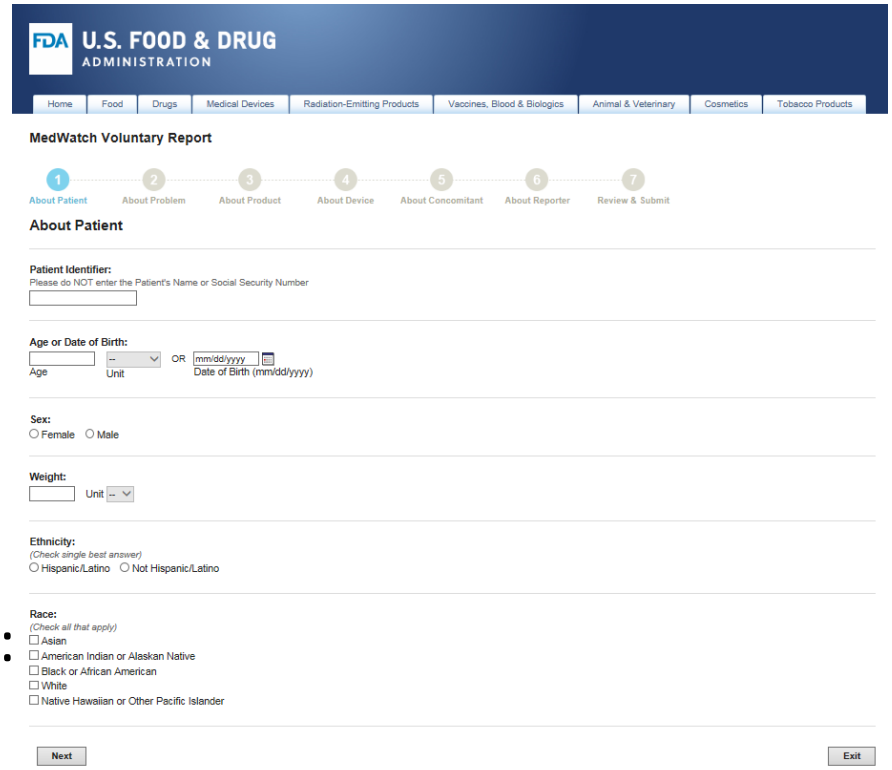
# Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Food and Drug Administration

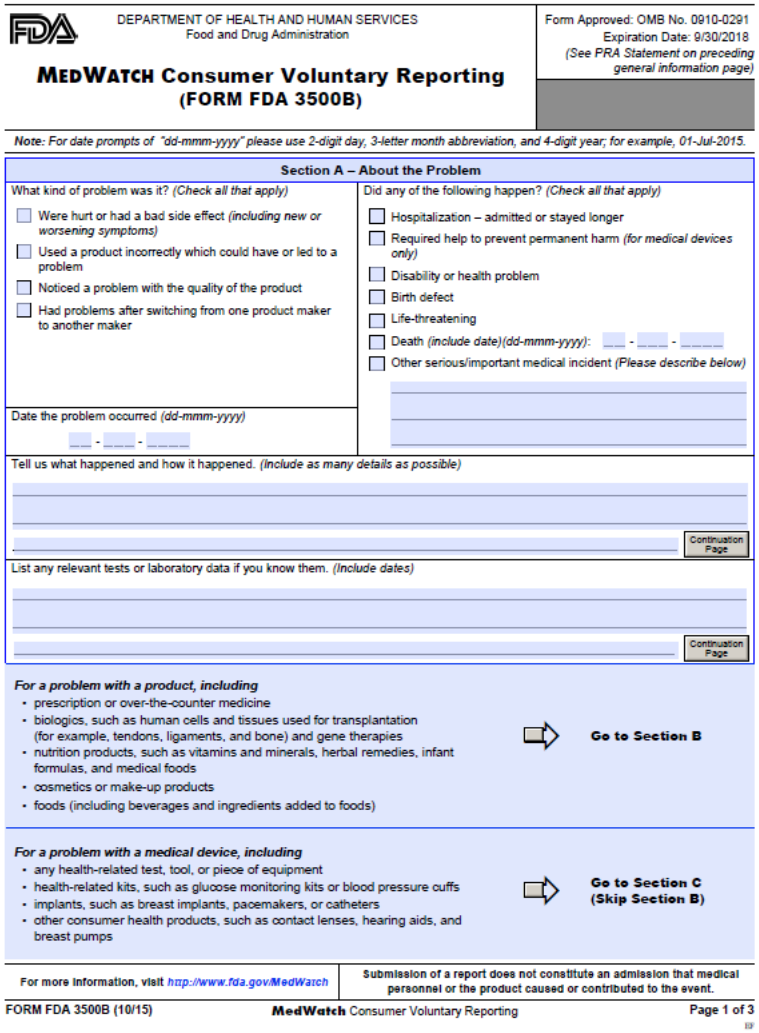
MEDWATCH

- 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

# Definition of Serious Outcomes

- Outcomes of:
  - 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)*

# 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)*