FDA Post-Marketing Drug Safety Surveillance

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Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
March 7, 2017

Objectives

- Define pharmacovigilance and adverse drug reactions
- Describe the Division of Pharmacovigilance (DPV)
- Identify the components of post-marketing drug safety surveillance
- Cite regulatory requirements and the role of MedWatch for reporting post-marketing safety information
- Summarize how adverse event reports are collected and analyzed by FDA/CDER/DPV

Outline

- Pharmacovigilance Background
- Post-marketing Surveillance
- Spontaneous Adverse Event Reports and the FDA Adverse Event Reporting System (FAERS)
- Signal Detection
- Components of a Good Case Report
- Case Series Development and Evaluation

Pharmacovigilance

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

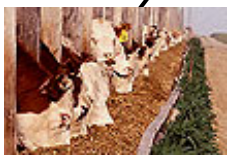
* The Importance of Pharmacovigilance, World Health Organization 2002

Adverse Drug Experience as Defined by Regulation (21 CFR 314.80)

Any undesirable event that is associated with the use of a drug in humans, whether or not considered drug-related. This may include:

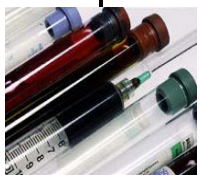
- Occurring in the course of the use of a drug product in professional practice
- Drug overdose
- Drug abuse
- Drug withdrawal
- Any failure of expected pharmacologic action

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)**



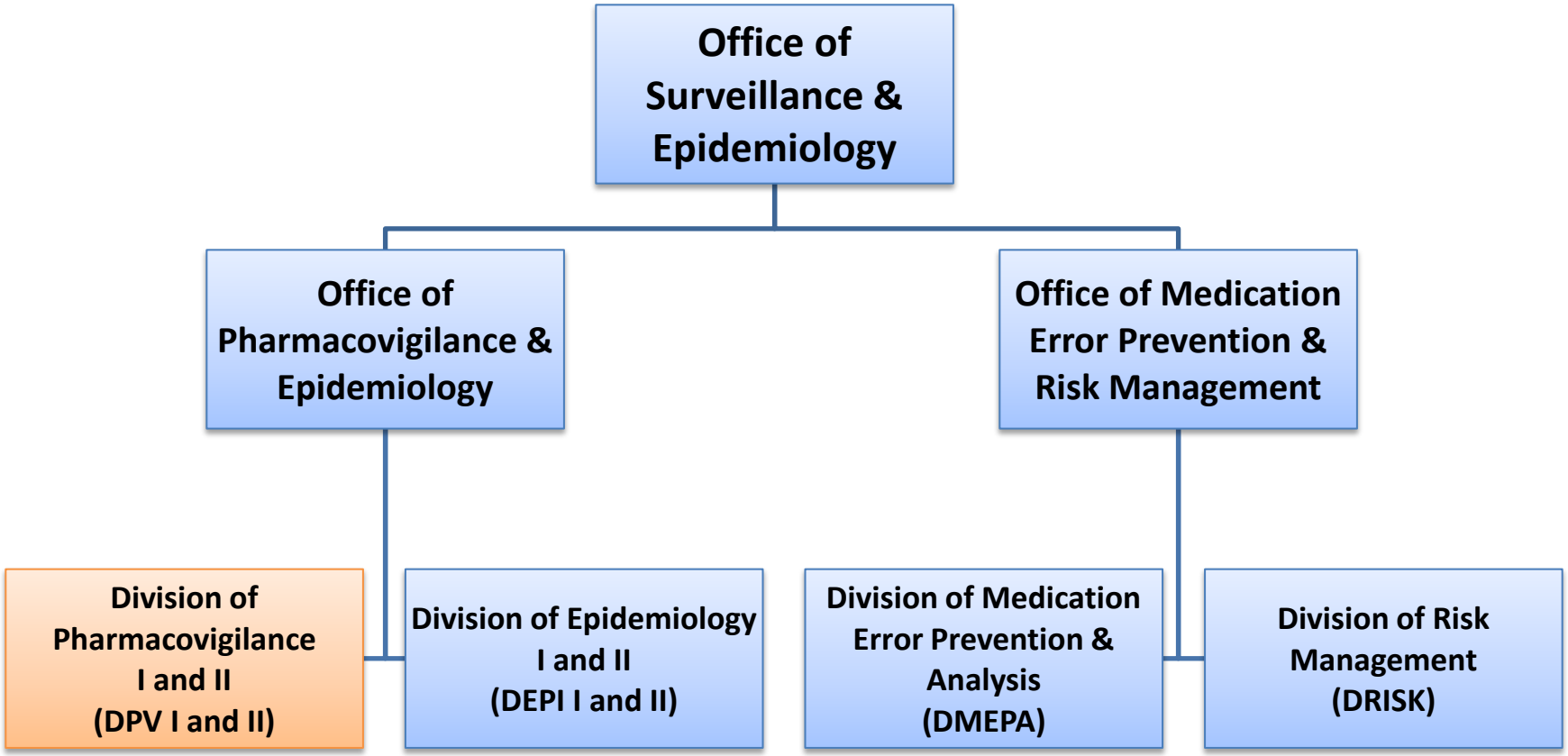
Center for **B**iologics **E**valuation & **R**esearch **(CBER)**

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

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

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

Office of Surveillance & Epidemiology

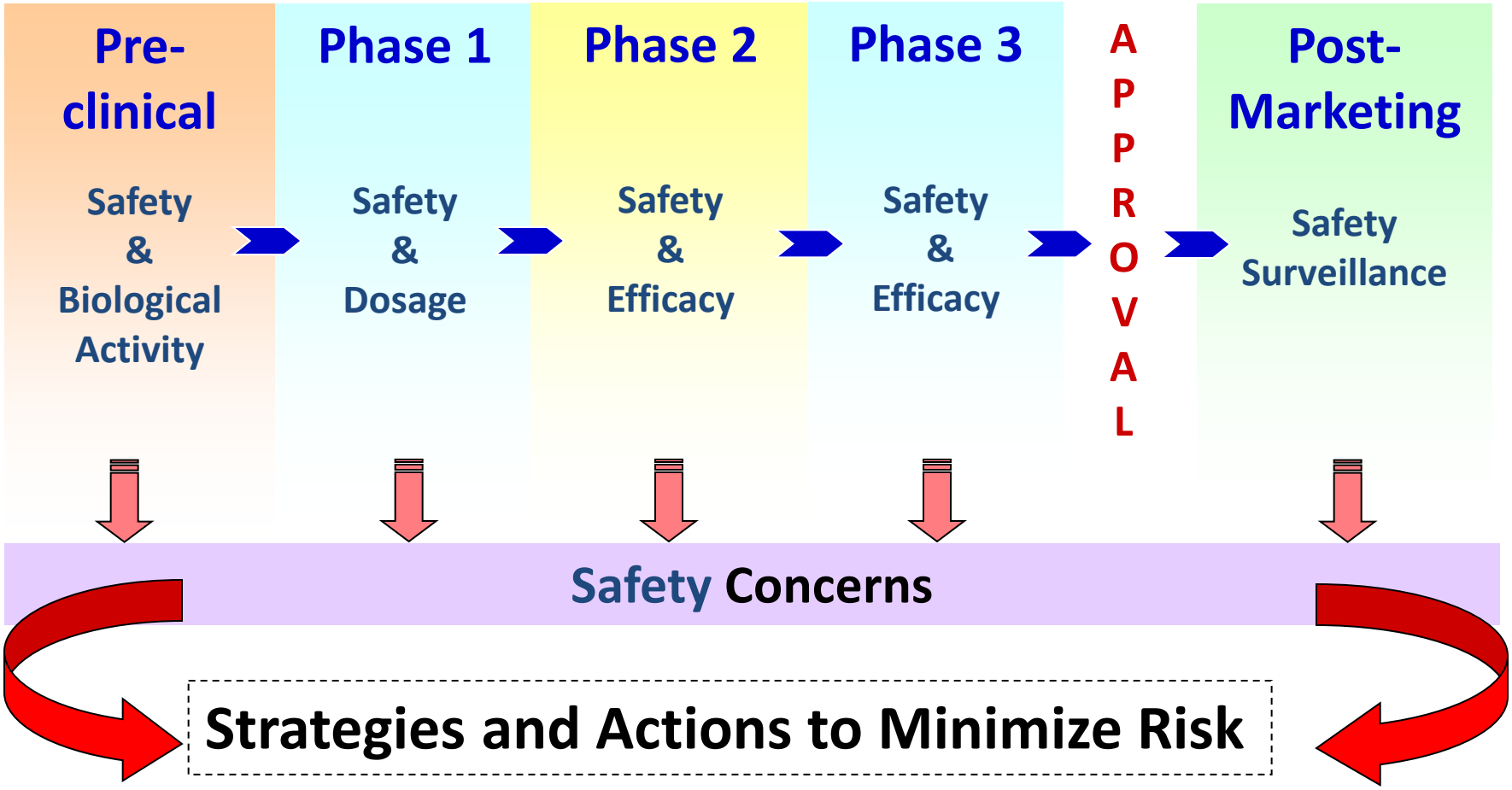


Divisions of Pharmacovigilance

- Evaluate the safety of drug and therapeutic biologic products
- Analyzing safety signals
- Recommend regulatory actions
- Communicate relevant safety information

Post-Marketing Surveillance

Safety in the Lifecycle of FDA-regulated Products



Limitations of Pre-Approval Clinical Trials

- Trial population
  - Size
    - Trial population vs. treated population
  - Narrow
    - Very young or very old usually not enrolled
  - Co-morbidities
    - Hepatic or renal failure
    - Other serious medical conditions
    - Use of concomitant medications
- Indications for use
  - Proposed indication for use
    - Patients at complex disease stages often not enrolled
- Duration of trial
  - Typical chronic use (years) vs. trial (several weeks to months)

Safety Monitoring during the Post-Approval Phase of a Drug Product's Life Cycle

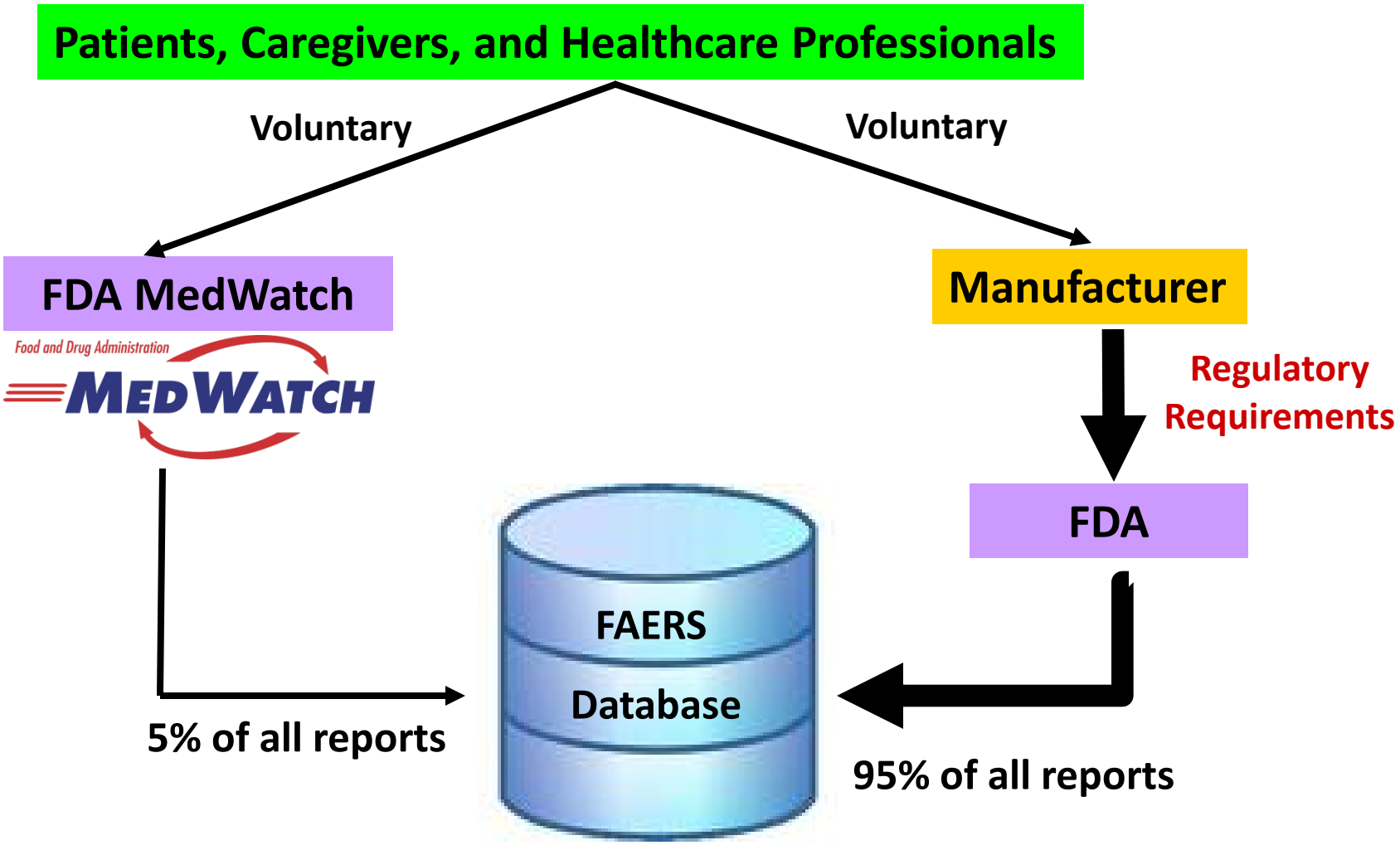
- Less frequent adverse drug experiences (ADEs)
- Patients with higher risk for ADEs
- Chronic and long term use
- Drug-drug interactions
- Drug-food interactions
- Expected ADEs
  - Increased severity or frequency
- Misuse or abuse of drug product
- Medication errors
  - Product packaging, labeling, other characteristics

Types of Post-Marketing Adverse Event Data

- Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Local or Regional (Joint Commission Requirement)
  - Scientific literature publications
- Post-marketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials
- Active surveillance
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel initiative

Post-marketing Adverse Event Reporting and MedWatch

How Post-marketing Reports Get to FDA



Post-marketing safety reporting requirements

- Under 21 CFR 314.80 post-marketing safety reports must be submitted to the agency for the following:
  - **15-day Alert reports**: **Serious** and **unexpected** adverse experience from all sources (domestic and foreign)
  - **Periodic Adverse Events 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

Serious Adverse Experience

- Results in any of these outcomes:
  - Death
  - Life-threatening adverse experience
  - Inpatient hospitalization – new or prolonged
  - Persistent/significant disability/incapacity
  - Congenital birth defect
  - Other serious: based upon appropriate medical judgment, they may jeopardize the patient and require intervention to prevent a serious outcome

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

Spontaneous Reports and FAERS

Spontaneous Reports

- A communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority
- Describes a suspected adverse event(s)
- Passive and voluntary reports

Spontaneous Reporting System Strengths

- Relatively affordable system to monitor all drugs
- Can report even if causality is uncertain
- Less restrictive than clinical trials
  - Reports can be submitted for any drug, old and new
  - Entire US population is “eligible”
- Reports emerge from usual healthcare settings
  - Patient and prescriber population more heterogeneous
  - All stages of treated disease
  - Longer duration of use
  - Captures “off-label” use, including diagnosis and dose
  - Co-morbidities, concomitant products and procedures

Spontaneous Reporting System Limitations

- Passive, voluntary surveillance
- Underreporting occurs and is variable from drug to drug and over time
  - Some literature cites 1-10%
  - Actual is unknown so FDA does not assume extent
- Reporting bias exists
- Quality of the reports is variable and often incomplete
- Duplicate reporting of the same case occurs
- Not population-based data source
  - Can not reliably estimate incidence or prevalence
  - numerator uncertain, denominator can only be projected from drug utilization data

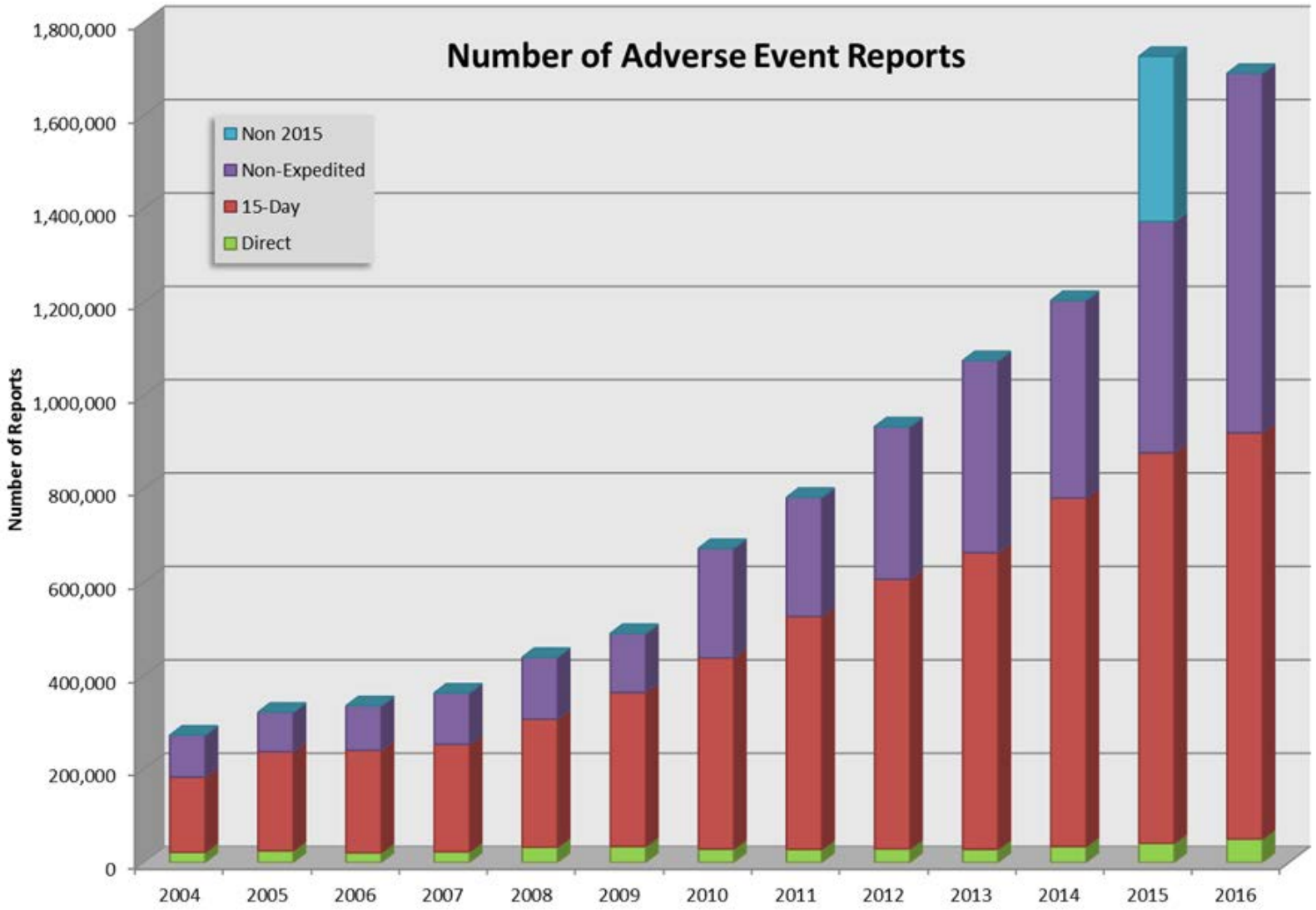
Factors Affecting Reporting

- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event
- Type of drug product and indication
- Length of time on market
- Extent and quality of manufacturer's surveillance system
- Prescription or over-the counter (OTC) product status
- Reporting regulations

FDA Adverse Event Reporting System

- Fully automated computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- ~13 million reports since 1969
- Over 1.69 million new reports in 2016

Number of Adverse Event Reports Entered into FAERS



Best Applications of FAERS

- Events that are linked to specific diagnoses
- Events with a serious outcome that rarely occur in an untreated population
- Events with a short-to-moderate latency period following exposure
- “Safety signal” generation and descriptive case series

What is a Safety Signal?

- Reported information on a possible causal relationship between an adverse event and a drug
- The relationship being 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

Components of a Good Case Report

Case #1

A health care worker reported a male patient started Drug X at 5 mg daily for type 2 diabetes on February 11, 2016. On an unknown date, the patient developed liver failure; additional information was not provided.

Case #2

- 59-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of liver disease.
- Started Drug X on February 11, 2016.
- Other medications: simvastatin and lisinopril.
- Labs drawn on Feb 11 revealed liver enzymes, INR, creatinine, and bilirubin all within normal limits.
- No alcohol use.
- 8 weeks after starting Drug X patient presented to ER with 5 day history of jaundice, dark urine, and nausea/vomiting.
- He was admitted to ICU and subsequently diagnosed with acute liver failure.
- Drug X stopped upon admission.
- Viral hepatitis was ruled out.
- 7 days after stopping the medication, all lab values returned to normal.

Components of a Good post-marketing 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

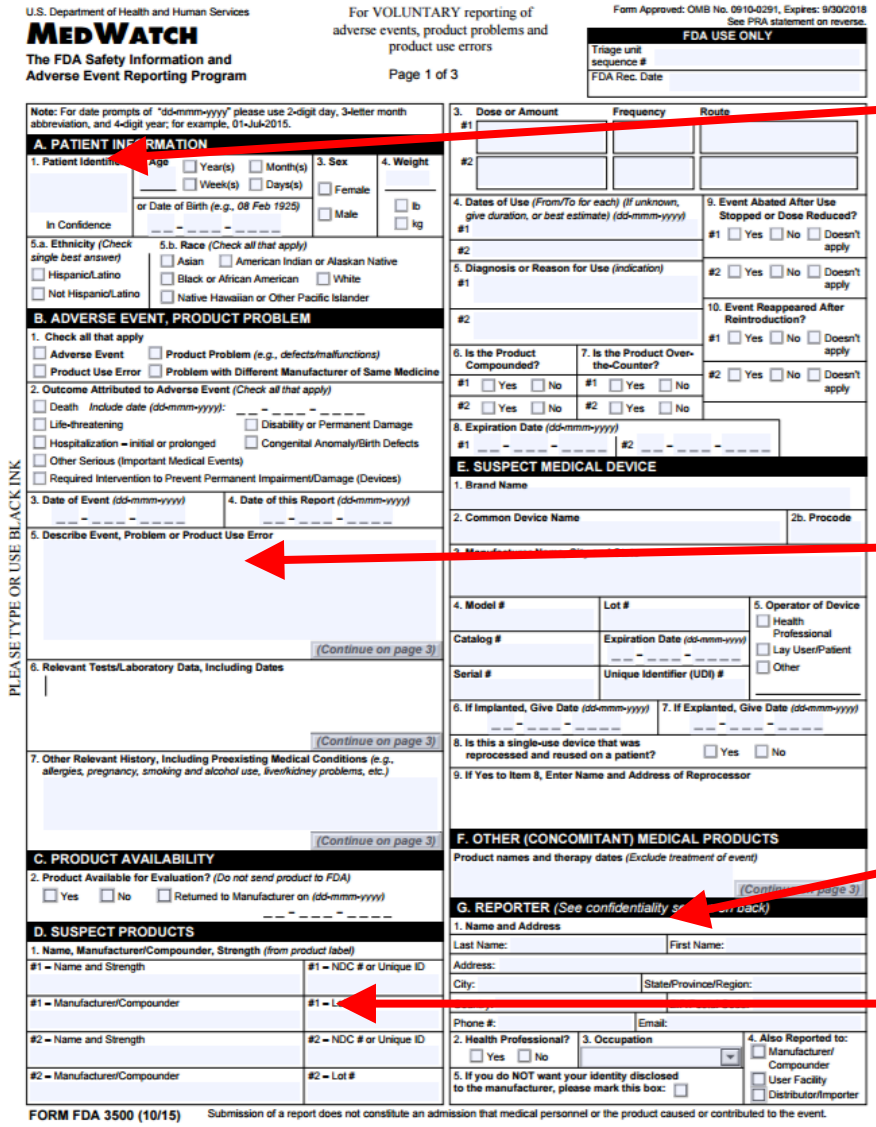
Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005

Evaluation of Case Reports

- Adverse event occurrence in expected time
- Absence of symptoms prior to exposure
- Positive dechallenge or rechallenge
- Consistent with pharmacologic effects
- Consistent with known effects in the class
- Support from pre-clinical studies, clinical trials
- Absence of alternative explanations

How to Report to MedWatch

Reporting to MedWatch



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 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

FDA USE ONLY
Triage unit sequence #
FDA Rec. Date

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.

A. PATIENT INFORMATION
1. Patient Identifier / In Confidence
Age ☐ Year(s) ☐ Month(s) ☐ Week(s) ☐ Days(s)
or Date of Birth (e.g., 08 Feb 1925)
3. Sex ☐ Female ☐ Male
4. Weight ☐ lb ☐ kg
5.a. Ethnicity (Check single best answer) ☐ Hispanic/Latino ☐ Not Hispanic/Latino
5.b. Race (Check all that apply) ☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM
1. Check all that apply
☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine
2. Outcome Attributed to Adverse Event (Check all that apply)
☐ Death Include date (dd-mmm-yyyy): ☐ Life-threatening ☐ Hospitalization – initial or prolonged ☐ Other Serious (Important Medical Events) ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices) ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event, Problem or Product Use Error
(Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. PRODUCT AVAILABILITY
2. Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on (dd-mmm-yyyy)

D. SUSPECT PRODUCTS
1. Name, Manufacturer/Compounder, Strength (from product label)

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

3. Dose or Amount / Frequency / Route
#1
#2
4. Dates of Use (From/To for each) (If unknown, give duration, or best estimate) (dd-mmm-yyyy)
#1
#2
5. Diagnosis or Reason for Use (indication)
#1
#2
6. Is the Product Compounded? #1 ☐ Yes ☐ No #2 ☐ Yes ☐ No
7. Is the Product Over-the-Counter? #1 ☐ Yes ☐ No #2 ☐ Yes ☐ No
8. Expiration Date (dd-mmm-yyyy) #1 #2
9. Event Abated After Use Stopped or Dose Reduced? #1 ☐ Yes ☐ No ☐ Doesn't apply #2 ☐ Yes ☐ No ☐ Doesn't apply
10. Event Reappeared After Reintroduction? #1 ☐ Yes ☐ No ☐ Doesn't apply #2 ☐ Yes ☐ No ☐ Doesn't apply

E. SUSPECT MEDICAL DEVICE
1. Brand Name
2. Common Device Name
2b. Procode
4. Model #
Lot #
5. Operator of Device ☐ Health Professional ☐ Lay User/Patient ☐ Other
Catalog #
Expiration Date (dd-mmm-yyyy)
Serial #
Unique Identifier (UDI) #
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? ☐ Yes ☐ No
9. If Yes to Item 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS
Product names and therapy dates (Exclude treatment of event)
(Continue on page 3)

G. REPORTER (See confidentiality statement on back)
1. Name and Address
Last Name: First Name:
Address:
City: State/Province/Region:
Phone #: Email:
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to: ☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/15) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Patient Identifier

Event or Problem

Reporter

Product

FDA U.S. FOOD & 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

Case Series Development and Evaluation

Development of a Case Series

- Identify a well-documented case from FAERS, published literature, data mining, or other sources to identify a safety signal.
- Using our knowledge of the clinical course of the disease, formulate a case definition which may include both clinical features and laboratory findings, sometimes even demographic information if we believe the safety signal is for a specific population.
- Complete a thorough database search for additional cases.

Development of a Case Series

Step 1

- **Identify a well-documented case (or cases) in FAERS, published literature or other source that supports a safety signal**

Step 2

- **Formulate a case definition**

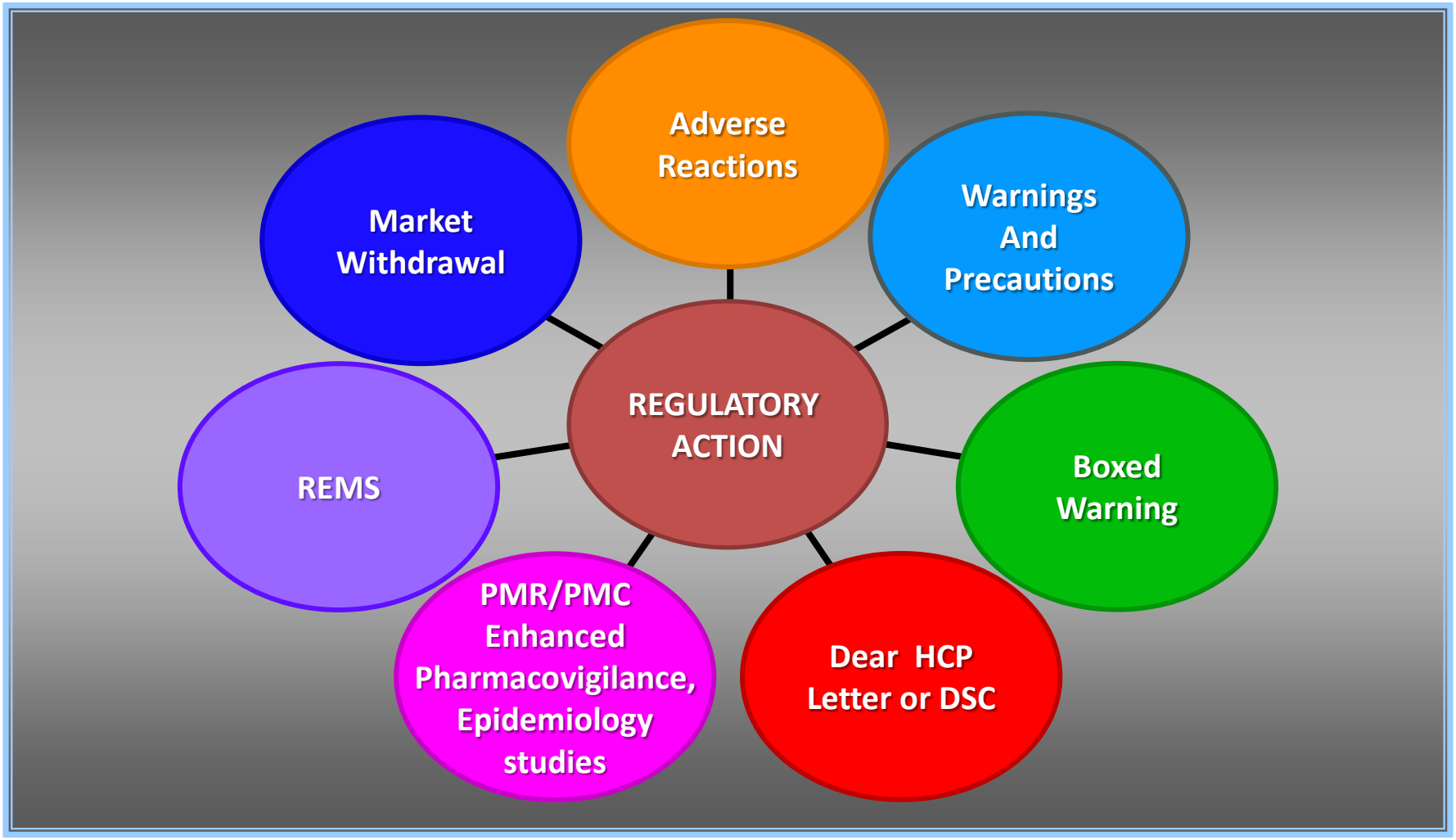
Step 3

- **Search for additional cases using:**
  - **FAERS**
  - **Published literature**
  - **Clinical Trial Adverse Event Data**
  - **Other databases**

Example: Aripiprazole and Impulse Control Problems

- Case definition excluded patients with history of impulse control disorders, concurrent substance abuse, or symptoms of mania
- 167 cases found in FAERS
- 17 cases found in medical literature
- All had a temporal relationship with aripiprazole
- All had a positive dechallenge
- Four rechallenge cases, all positive

Regulatory Actions



Regulatory Actions

- Product information changes – Warnings, Precautions, Adverse Reactions
- Pharmacovigilance activities - enhanced surveillance (e.g., expedited reporting), registry, epidemiology studies
- Risk Evaluation and Mitigation Strategy (REMS)
  - Communication plan, restricted use
- Drug Safety Communication (DSC)
- Market withdrawal

Communicating Safety Issues

Communicating Safety Issues to the Public and Internationally

- MedWatch Safety Alerts
- Postmarket Drug and Biologic Safety Evaluations (FDAAA 915)
- Potential Signals of Serious Risks/New Safety Information Identified from FAERS (FDAAA 921)
- Published literature and scientific meetings
- Video and teleconferences with foreign regulatory agencies:
  - EMA: European Medicines Agency
  - 4-Way: Canada, Australia, New Zealand, (Singapore in writing)

MedWatch: The FDA Safety Information and Adverse Event Reporting Program

Your FDA gateway for clinically important safety information and reporting serious problems with human medical products.

MedWatch The FDA Safety Information and Adverse Event Reporting Program

- Subscribe to MedWatch Safety Alerts
- Safety Information
- Reporting Serious Problems to FDA

Resources for You

- 2016 Safety Alerts for Human Medical Products
- Contact Information For Voluntary Adverse Event Reporting
- MedWatchLearn - Teaching students, health professionals, and consumers how to report problems to FDA
- Medical Product Safety Educational Resources
- Consumer-Friendly Reporting Form 3500B (PDF - 1.2MB)

Report a Problem | **Safety Information** | **Stay Informed**

What's New

- I.V. Flush Syringes by Nurse Assist: Recall - Potential Link to Burkholderia Cepacia Bloodstream Infections UPDATED 01/04/2017 Recall classified as Class I. The effects of Burkholderia cepacia on people vary widely, ranging from no symptoms at all to serious respiratory infections, especially in patients with cystic fibrosis. Priginally Posted 10/05/2016

More What's New

FDA Approved Safety Information

- DailyMed (National Library of Medicine)
  Current Drug Prescribing Information. (NOTE: Drugs marked "unapproved" on this site have not been reviewed by FDA for safety and efficacy, and their labeling has not been approved.)
- Medication Guides
  Paper handouts that come with many prescription medicines. Medication Guides address issues specific to particular drugs and drug classes. They contain FDA-approved information that can help patients avoid serious adverse events.
- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)
- Postmarket Drug and Biologic Safety Evaluations
  Evaluations performed 18 months after drug approval, or after its use by 10,000 individuals.

Recent Drug Safety Communications

- Canagliflozin, dapagliflozin and acute kidney injury (June, 2016)
- High-dose loperamide and serious heart problems (June, 2016)
- Over-the-counter antacid products containing aspirin and serious bleeding risk (June, 2016)
- Fluoroquinolone antibiotics and disabling side effects (May, 2016)
- Olanzapine and serious skin reactions (May, 2016)
- Aripiprazole and impulse-control problems (May, 2016)

www.fda.gov/MedWatch

Report a Problem | Safety Information | Stay Informed

Questions

References

- Arthur N et al. The Importance of Pharmacovigilance – Safety Monitoring of Medicinal Products. WHO 2002.
- Drug Safety Communications: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm
- FDA Patient Safety News: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/index.cfm
- Guidance for Industry- post-marketing Safety Reporting for Human Drug and Biological Products including Vaccines, March 2001: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm
- Guidance for Industry- Good Pharmacovigilance Practices and Pharmacoepiemiologic Assessment, March 2005: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program: http://www.fda.gov/Safety/MedWatch/default.htm
- MedWatch Medical Product Safety Information: http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm
- MedWatch Safety Alerts: http://www.fda.gov/Safety/MedWatch/ucm287881.htm
- MedWatch Safety Alert RSS Feed: http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/MedWatch/rss.xml
- Postmarket Drug Safety Information for Patients and Providers (FDAAA 915): http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm
- post-marketing Drug and Biologic Safety Evaluations: (FDAAA 915): http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm
- Potential Signals of Serious Risks/New Safety Information Identified from AERS (FDAAA 921): http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm#QuarterlyReports

Acronyms

- CDER – Center for Drugs Evaluation & Research
- CFR – Code of Federal Regulations
- DEPI I & II – Division of Epidemiology I & II
- DILIN – Drug-Induced Liver Injury Network
- DMEPA – Division of Medication Error & Prevention Analysis
- DPV I & II – Division of Pharmacovigilance I & II
- DRISK – Division of Risk Management
- DSC – Drug Safety Communication
- EMA – European Medicines Agency
- FDA – Food & Drug Administration

Acronyms, cont'd

- FDAAA – Food & Drug Administration Amendment Act
- FAERS – FDA Adverse Events Reporting System
- HCP – Health Care Provider
- MO – Medical Officer
- NDA – New Drug Application
- OND – Office of New Drugs
- PMC – post-marketing Commitment
- PMR – post-marketing Requirement
- REMS – Risk Evaluation & Mitigation Strategy
- SE – Safety Evaluator
- WHO-UMC – World Health Organization – Uppsala Monitoring Centre