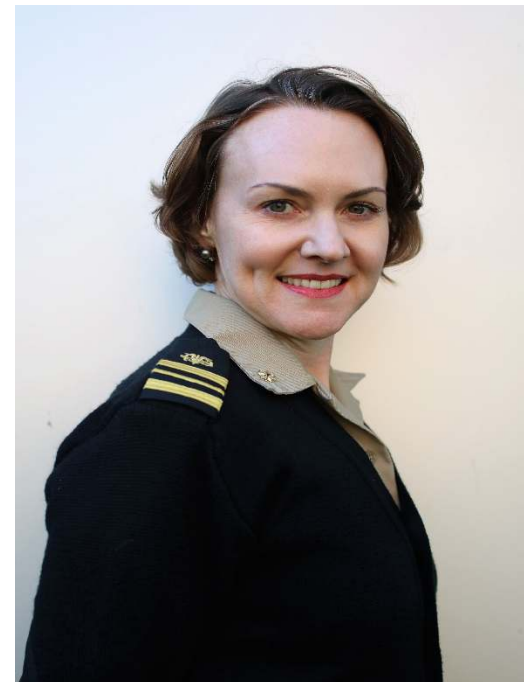




An Introduction to Drug Safety Surveillance and the FDA Adverse Event Reporting System

LTCDR Anne Tobenkin, PharmD

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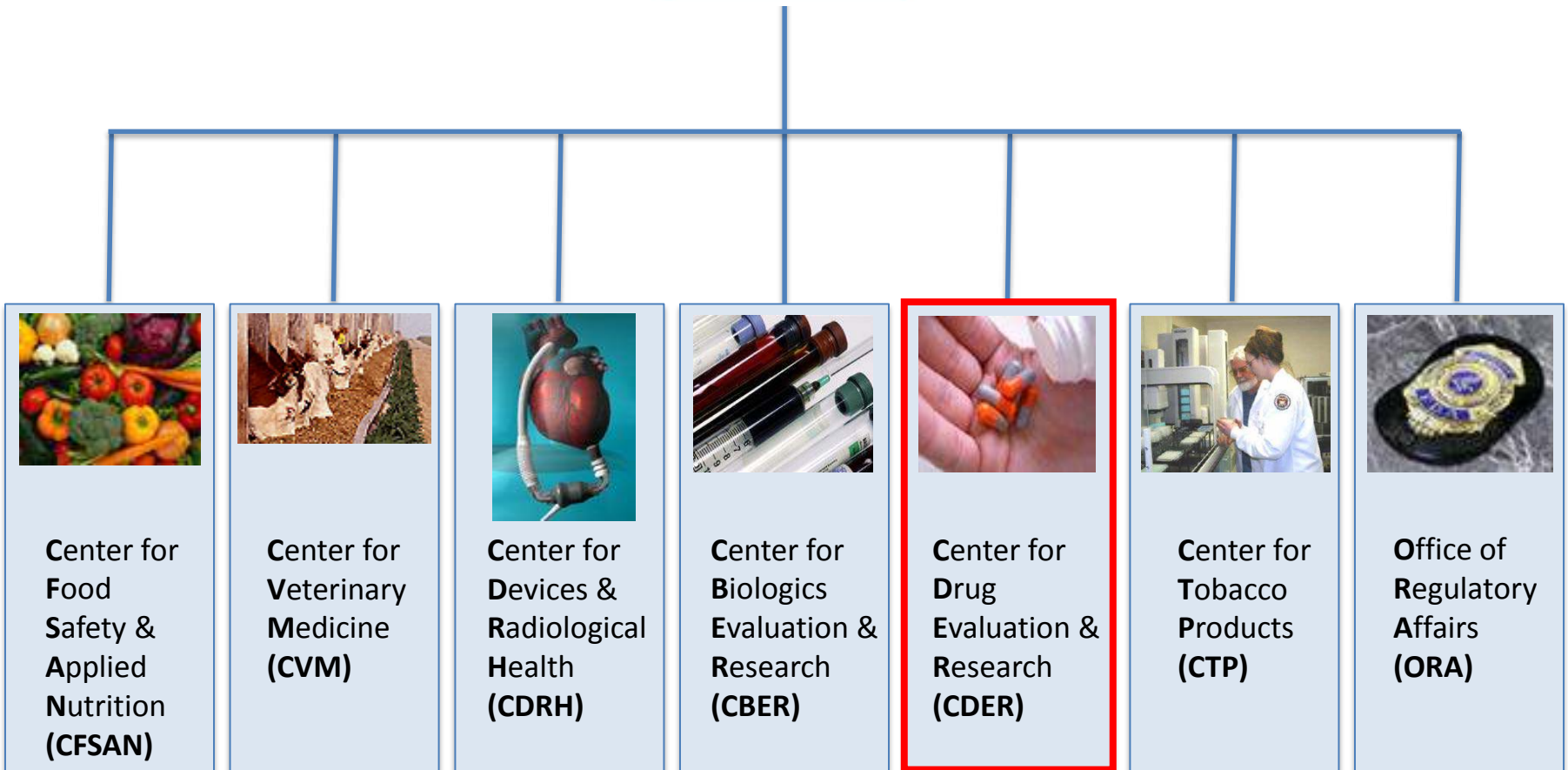


Objectives

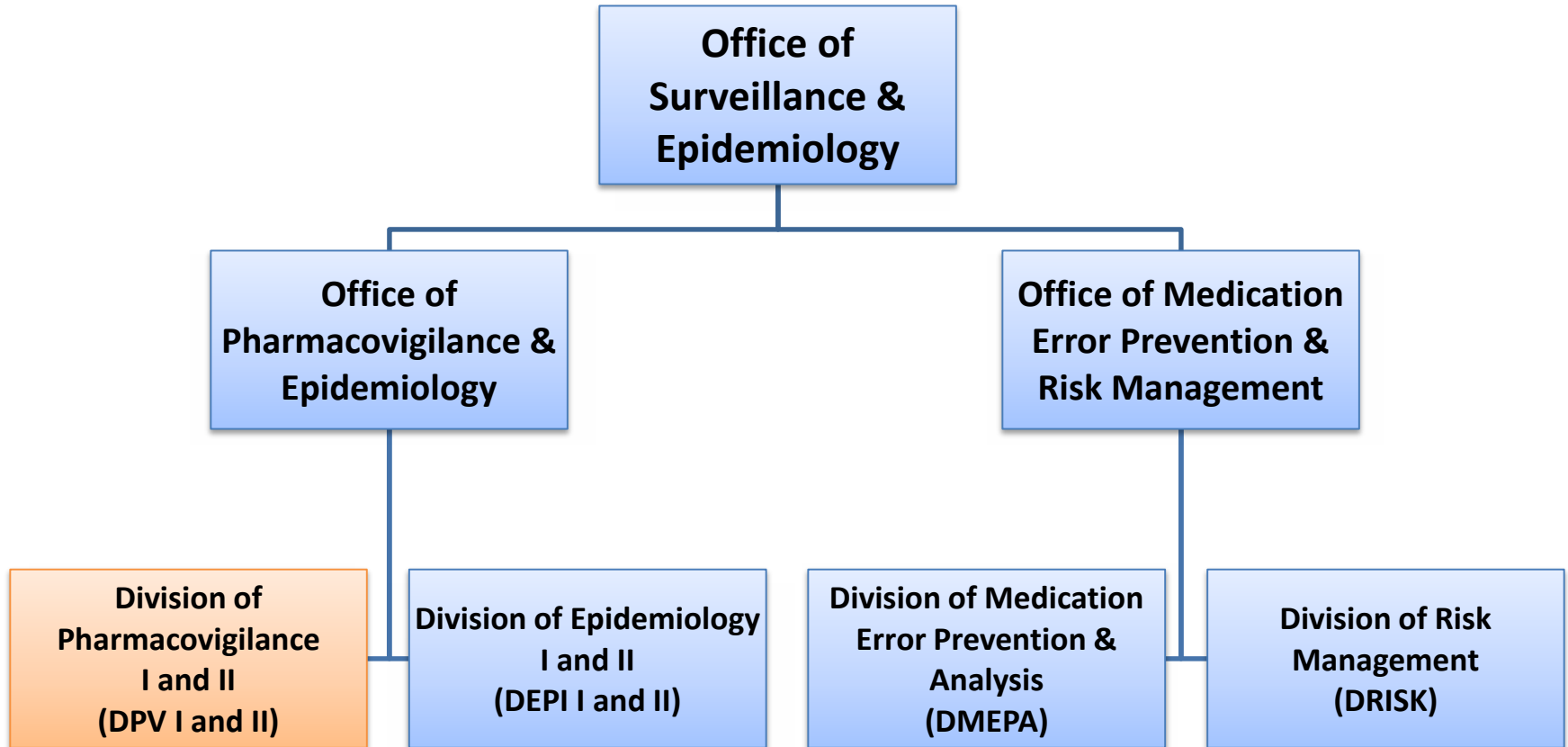
- Define pharmacovigilance and adverse drug reactions (ADR)
- Describe the Division of Pharmacovigilance (DPV)
- Characterize postmarketing drug safety surveillance
- Explain regulatory requirements and the role of MedWatch for reporting postmarketing safety information
- Summarize how adverse event reports are collected and analyzed by FDA/DPV
- Describe how reports submitted by health care professionals (like yourselves) shape our working knowledge of the risks and benefits of drugs

Outline

- Pharmacovigilance background
- Postmarketing surveillance
- Postmarketing adverse event reports and the FDA Adverse Event Reporting System (FAERS)
- Safety signals and sources
- Elements of an informative case report
- Development and evaluation of a case series
- Example of a safety signal
- How to report an adverse event



Office of Surveillance & Epidemiology



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

Divisions of Pharmacovigilance

- Evaluate the safety of drug and therapeutic biologic products
- Monitoring/Surveillance
- Analyze safety signals
- Recommend regulatory actions
- Communicate relevant safety information

Evaluate

Monitor

Analyze

Action

Communicate

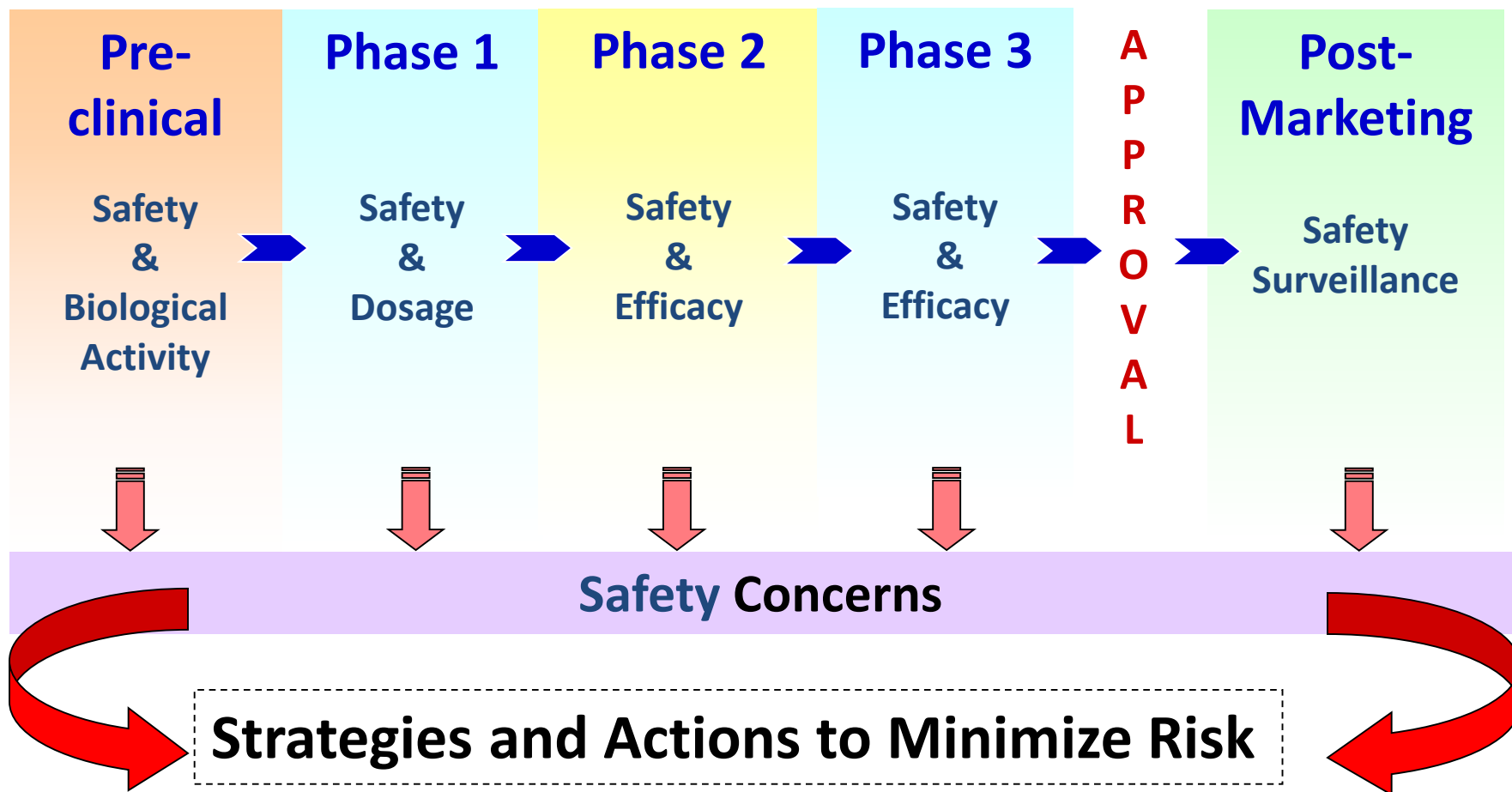
Division of Pharmacovigilance

- Nine teams of safety evaluators (SEs)
- Team coverage aligned with the Office of New Drugs (OND) review divisions' therapeutic areas
- Medical officers (MOs) provide clinical expertise in various therapeutic areas



Postmarketing 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)

Benefits of Postmarketing Monitoring

- Rare adverse experiences
- Adverse experiences among high risk groups
- 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

Postmarketing Adverse Event Reporting

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

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 and occurs in the course of the use of a drug product in professional practice. This may include:

- Drug overdose
- Drug abuse
- Drug withdrawal
- Any failure of expected pharmacologic action

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

Postmarketing Safety Reporting Requirements

- Under 21 CFR 314.80 postmarketing 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 Experience 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

Spontaneous Reports and FAERS

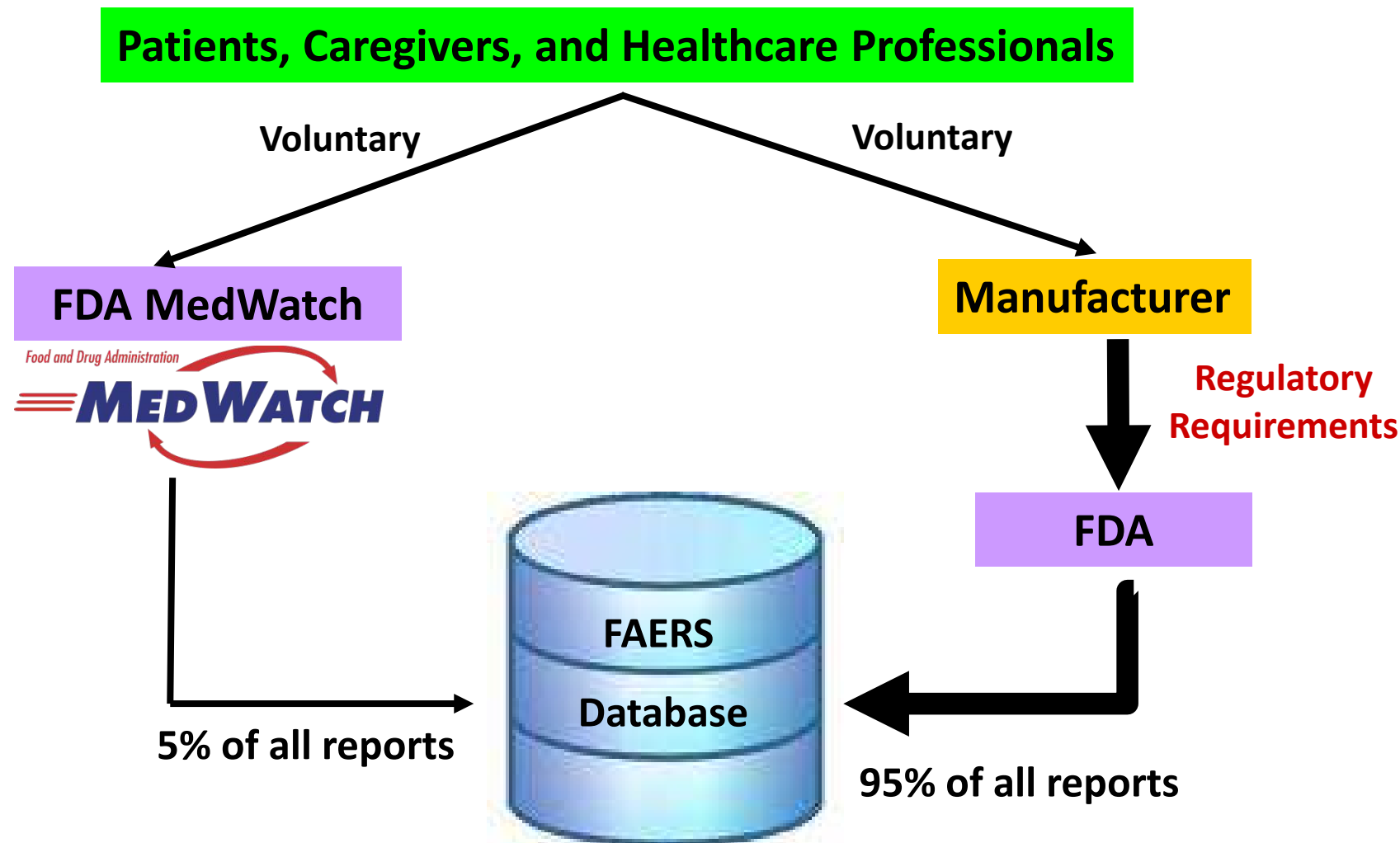


FDA Adverse Event Reporting System

- Fully automated computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- ~14 million reports since 1969
- Over 1.81 million new reports in 2017



How Postmarketing Reports Get to FDA



FAERS Strengths

- 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

FAERS 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

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

FAERS Public Dashboard:

<https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis>

FDA Adverse Events Reporting System (FAERS) Public Dashboard

[Home](#) [Search for Products](#)

[Disclaimer](#) [Site Feedback](#) [Report a Problem](#) [FAQ](#)

Total Reports
14,840,598

Serious Reports (excluding death)
8,434,750

Death Reports
1,491,711

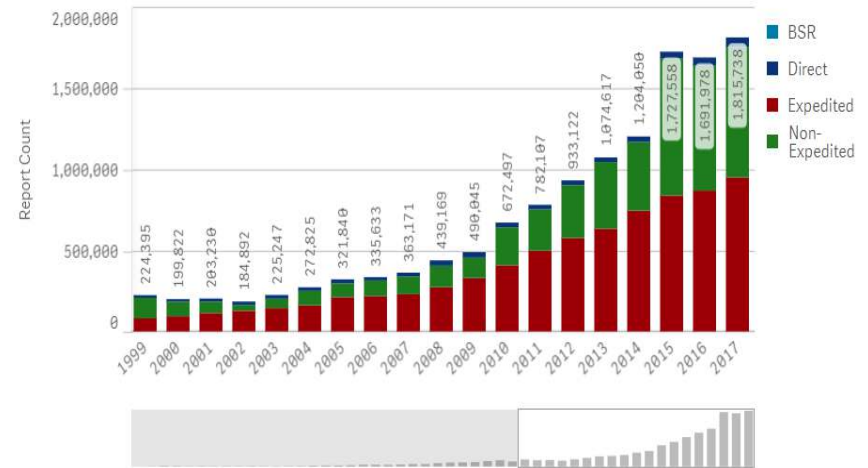
Reports by Report Type

[Since 1968](#) [Last 10 Years](#)

Reports received by Year and Report Type

Year	Category	Total Reports	Expedited	Non-Expedited	Direct	BSR
Total Reports		14,840,598	7,834,038	6,244,018	761,666	876
2017		1,815,738	951,656	803,516	60,566	-
2016		1,691,978	869,959	771,026	50,993	-
2015		1,727,558	839,197	846,702	41,659	-
2014		1,204,050	746,074	423,744	34,232	-
2013		1,074,617	634,816	411,411	28,390	-
2012		933,122	577,515	326,586	29,021	-
2011		782,107	498,832	255,232	28,043	-
2010		672,497	408,881	234,672	28,944	-
2009		490,045	329,707	126,172	34,166	-
2008		439,169	273,586	132,687	32,896	-
2007		363,171	225,247	110,404	22,022	-

Reports received by Year and Report Type



Data as of December 31, 2017

This page displays the number of adverse event reports received by FDA for drugs and therapeutic biologic products by the following Report Types.

- Direct Reports are voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals.
- Mandatory Reports are submitted by manufacturers and are categorized as:
 - i. Expedited reports that contain at least one adverse event that is not currently described in the product labeling and for which the patient outcome is serious, or

What is a Safety Signal?

Safety Signal

- Reported information on a possible causal relationship between an adverse event and a drug
- The relationship being previously unknown or incompletely documented
- Newly identified at-risk population
- New unlabeled adverse events
- An observed increase in a labeled event OR a greater severity or specificity
- New interactions
- Usually supported by multiple case reports

Postmarketing Signal Sources

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

Elements of an Informative Case Report and How to Report an Adverse Event

Four Requirements for a Case Report

- Patient
- Drug product
- Adverse event
- Reporter

Elements of an Informative 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

Case #1

- Health care worker reported
- Male patient
- Drug X at 5 mg daily for type 2 diabetes on February 11, 2017.
- The patient developed liver failure on an unknown date
- 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, 2017.
- 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.
- Reported by physician

Signal Detection, Development and Evaluation of Case Series

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

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

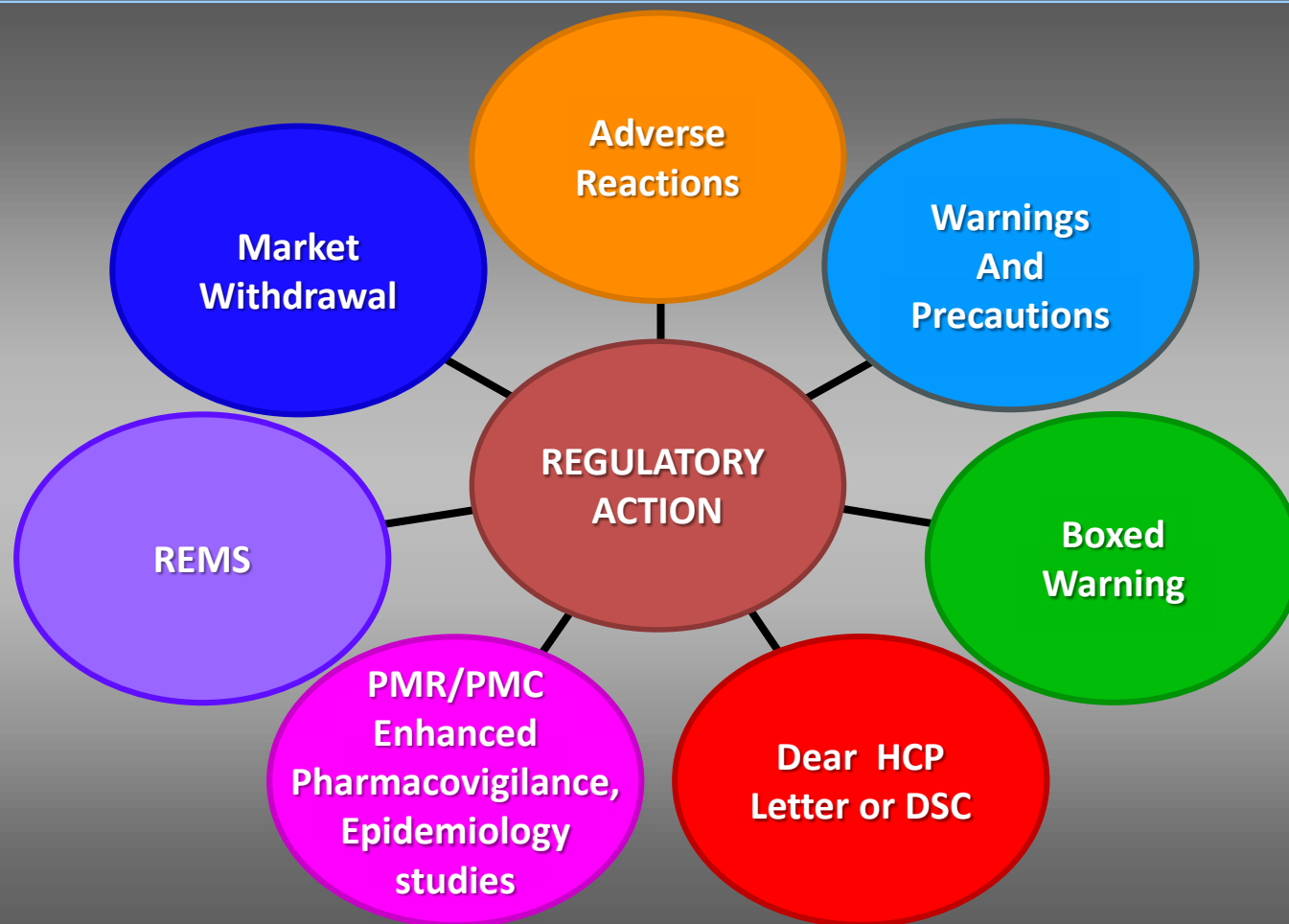
Characterization

So DPV identifies a safety signal – then what?

- | | |
|--|---|
| <ul style="list-style-type: none"> • Characterize the signal in a Safety Review <ul style="list-style-type: none"> – Written communication – Summary and analysis of a specific safety issue – Often results in recommendations for regulatory action | <ul style="list-style-type: none"> • Standard scientific format to document <ul style="list-style-type: none"> – Abstract – Background – Methods & Materials – Results – Discussion – Conclusion – Recommendations |
|--|---|

Regulatory Action and FDA Communications

Regulatory Actions



Communicating Safety Issues



Communicating Safety Issues to the Public and Internationally

- MedWatch Safety Alerts and Drug Safety Communications
- Potential Signals of Serious Risks/New Safety Information Identified from FAERS
- Published literature and scientific meetings
- Teleconferences with foreign regulatory agencies:
 - EMA: European Medicines Agency
 - International Post-Market Surveillance (IPMS): Canada, Australia, New Zealand, Switzerland, and Singapore (via written submissions)

Recent Drug Safety Communications

- Serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease (September, 2017)
- Increased risk of serious pancreatitis with irritable bowel drug Viberzi (eluxadoline) in patients without a gallbladder (March, 2017)
- Rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate (February, 2017)

An Example of Signal Identification, Characterization and Regulatory Action

Development and Characterization of Signal

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

Step 4

- Characterize the signal and recommend action

Journal Article



International Journal of Cardiology

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



Letter to the Editor

Life-threatening complete atrioventricular block associated with ticagrelor therapy



Alexander Goldberg^{a,b,*}, Inna Rosenfeld^c, Irena Nordkin^c, Majdi Halabi^{b,c}

^a Interventional Cardiology Unit, Ziv Medical Center, Zfat, Israel

^b Faculty of Medicine in Galilee, Bar-Ilan University, Zfat, Israel

^c Department of Cardiology, Ziv Medical Center, Zfat, Israel

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Keywords:

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

Ticagrelor Background

- Ticagrelor prevents platelet activation
- Indications:
 - Reduce the rate of cardiovascular death, myocardial infarction (MI) and stroke in patients with acute coronary syndrome (ACS) or a history of MI
 - Reduce the rate of stent thrombosis in patients who have been stented for treatment of ACS
- Dosage and Administration:
 - 180 mg loading dose then 90 mg twice daily for the first year then 60 mg twice daily thereafter
- Risk of bradycardia identified during a substudy

Example: Ticagrelor and atrioventricular block

- Case definition included AV block within one month of starting therapy and positive dechallenge or continued on therapy with a pacemaker
- 26 cases found in FAERS
- One case found in medical literature
- 15 patients had AV block < 24 hours after the first dose of ticagrelor

Ticagrelor Labeling

- WARNINGS AND PRECAUTIONS

- 5.5 Bradyarrhythmias

- Ticagrelor can cause ventricular pauses [see Adverse Reactions (6.1)]. Bradyarrhythmias including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from PLATO and PEGASUS and may be at increased risk of developing bradyarrhythmias with ticagrelor


How to Report to MedWatch:

<https://www.fda.gov/Safety/MedWatch/default.htm>





www.fda.gov/MedWatch

 **Report a Problem**

 **Safety Information**

 **Stay Informed**

Electronic Questionnaire

MedWatch Voluntary Report



About Problem

* Required Information

Adverse Event, Product Problem:

(Check all that apply)

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

Outcome Attributed to Adverse Event:

(Check all that apply)

- ☐ Death (include date) (mm/dd/yyyy)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability or Permanent Damage ?
- ☐ Congenital Anomaly/Birth Defects
- ☐ Other Serious (Important Medical Events)
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

Date of Event (mm/dd/yyyy):

mm/dd/yyyy

Conclusion

- Pharmacovigilance
- Postmarketing surveillance
- FAERS
- How we use postmarketing reports to identify safety information
- What information is useful for our analysis
- How we communicate our findings
- How you can report adverse events

Questions



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<http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/MedWatch/rss.xml>
- 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