

# *Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER*

LCDR Monica Muñoz, PharmD, MS, BCPS

Division of Pharmacovigilance

Office of Surveillance and Epidemiology

Center of Drug Evaluation and Research

February 23, 2016



# Objectives

- Define Pharmacovigilance
- Describe the Division of Pharmacovigilance's (DPV's) key safety roles in FDA's Center for Drug Evaluation and Research (CDER).
- Understand components of postmarketing drug safety surveillance.
- Understand regulatory requirements and the role of MedWatch for reporting postmarketing safety information.
- Describe how adverse event reports are collected and analyzed by FDA/CDER/DPV

# Outline

- Pharmacovigilance Background
- Postmarketing 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

# FDA



**Center for Food Safety & Applied Nutrition (CFSAN)**



**Center for Veterinary Medicine (CVM)**



**Center for Devices & Radiological Health (CDRH)**



**Center for Biologics Evaluation & Research (CBER)**



**Center for Drug Evaluation & Research (CDER)**

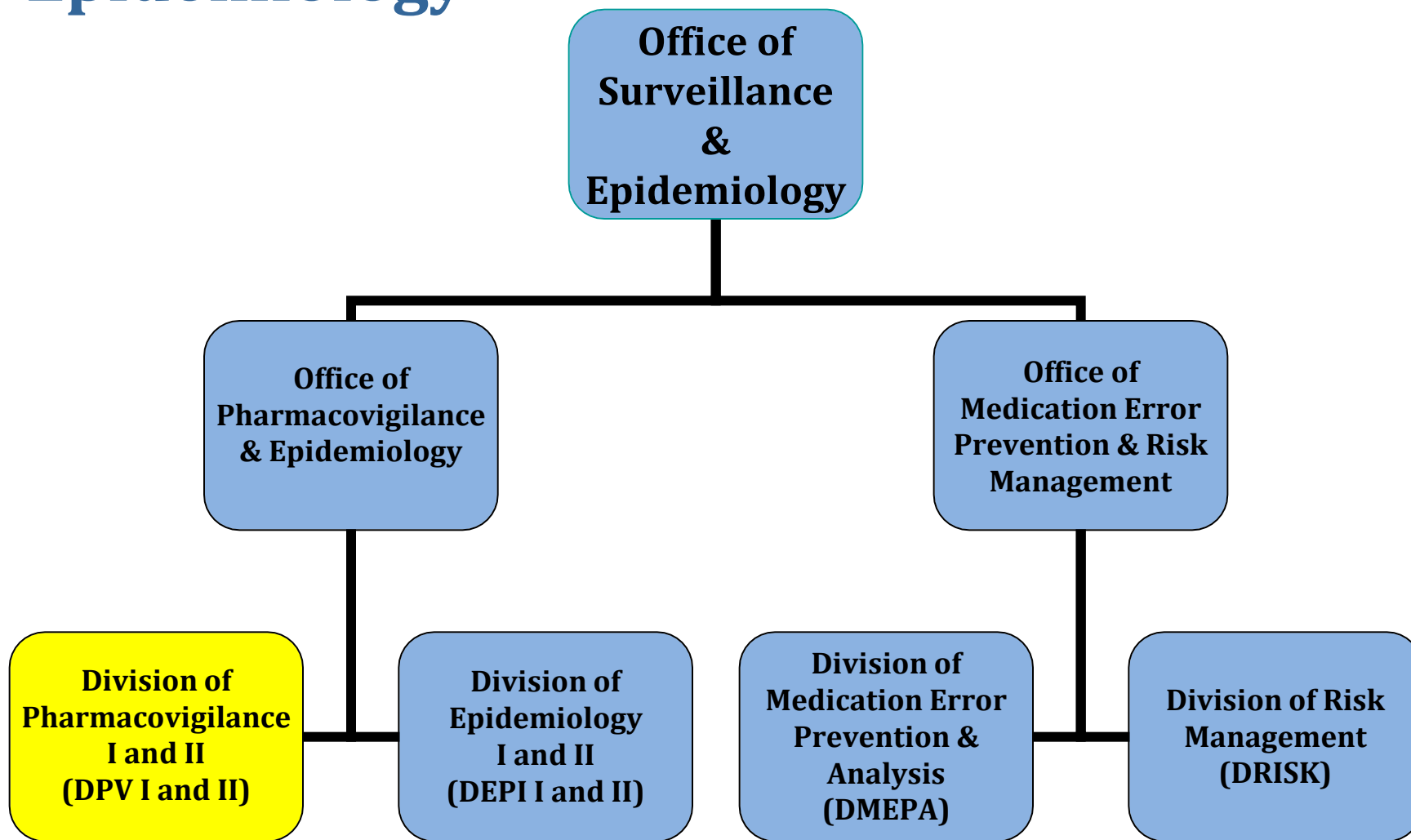


**Center for Tobacco Products (CTP)**



**Office of Regulatory Affairs (ORA)**

# 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
- Advance public health by detecting and analyzing safety signals from all available data sources, utilizing evidence-based methods
- Recommend appropriate regulatory actions, including labeling changes, Risk Evaluation and Mitigation Strategies (REMS), etc.
- Communicate relevant safety information



# Safety Evaluators (SEs)

- 10 teams of SEs
  - Majority clinical pharmacists
  - Provide critical analysis of sources of postmarketing data to identify and evaluate safety signals
- Team coverage aligned with the Office of New Drugs (OND) review divisions' therapeutic areas
  - ~ 4-7 SEs per team (including Team Leader)
  - Each SE covers assigned product group(s) aligned with therapeutic area



## Medical Officers (MOs)

- Provide clinical expertise in various therapeutic areas such as dermatology, oncology, rheumatology, etc.
- Collaborate with DPV teams on safety evaluation
- Collaborate with Office of New Drugs (OND) on safety evaluation



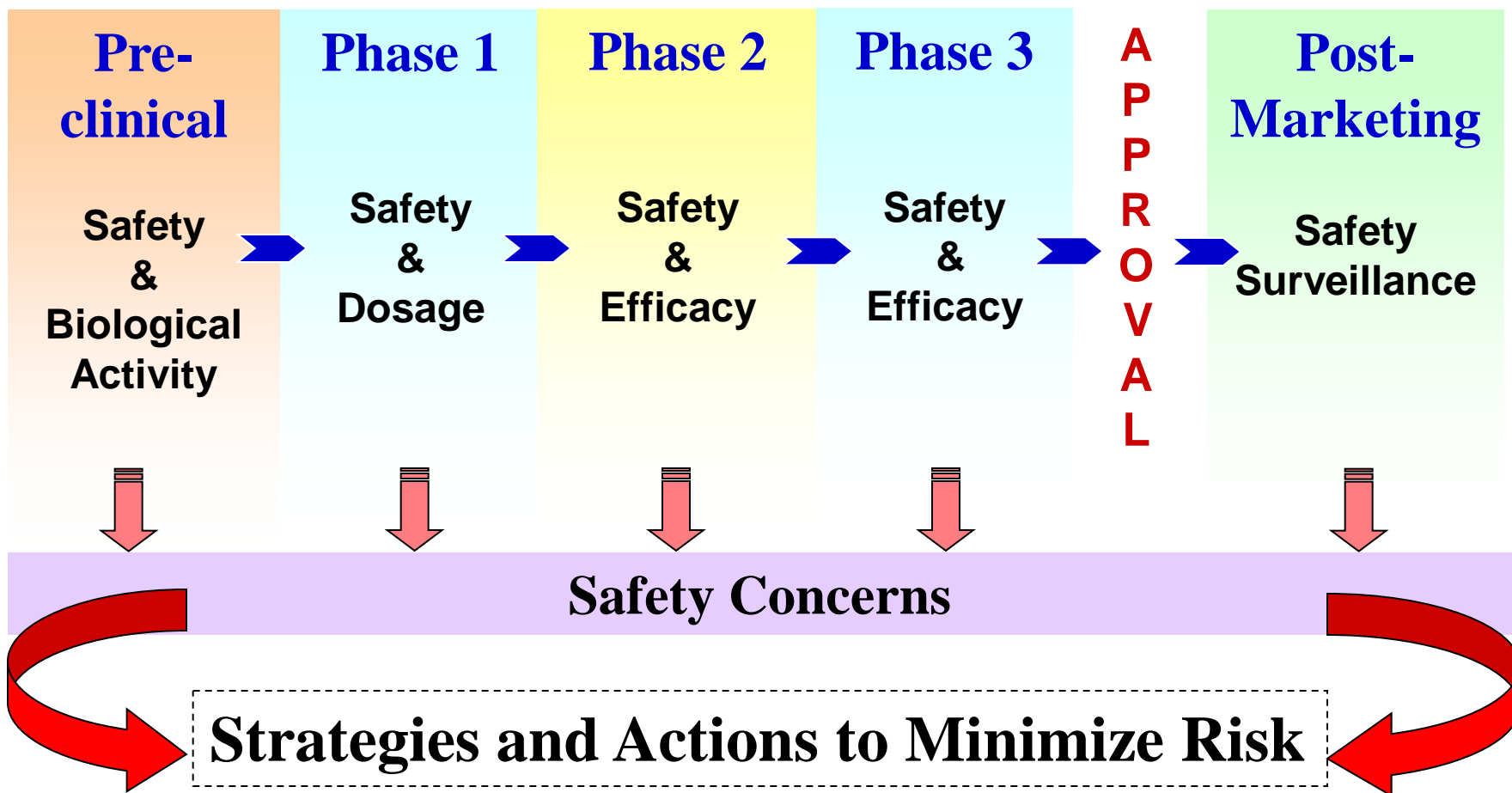
# Postmarketing Surveillance

# Challenge Question #1

## True or False

Safety data is only collected during the later phases of the clinical development program for a medical product.

# Safety in the Lifecycle of FDA-regulated Products



# Limitations of Premarketing Clinical Trials

- Size of the patient population studied
- Narrow population - often not providing sufficient data on special groups
- Narrow indications studied
- Short duration

# Benefits of Postmarketing Monitoring

The ability to study the following:

- Low frequency reactions (not identified in clinical trials)
- High risk groups
- Long-term effects
- Drug-drug/food interactions
- Increased severity and / or reporting frequency of known reactions

# Types of Postmarketing Surveillance

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

# Postmarket Adverse Event Reporting and MedWatch



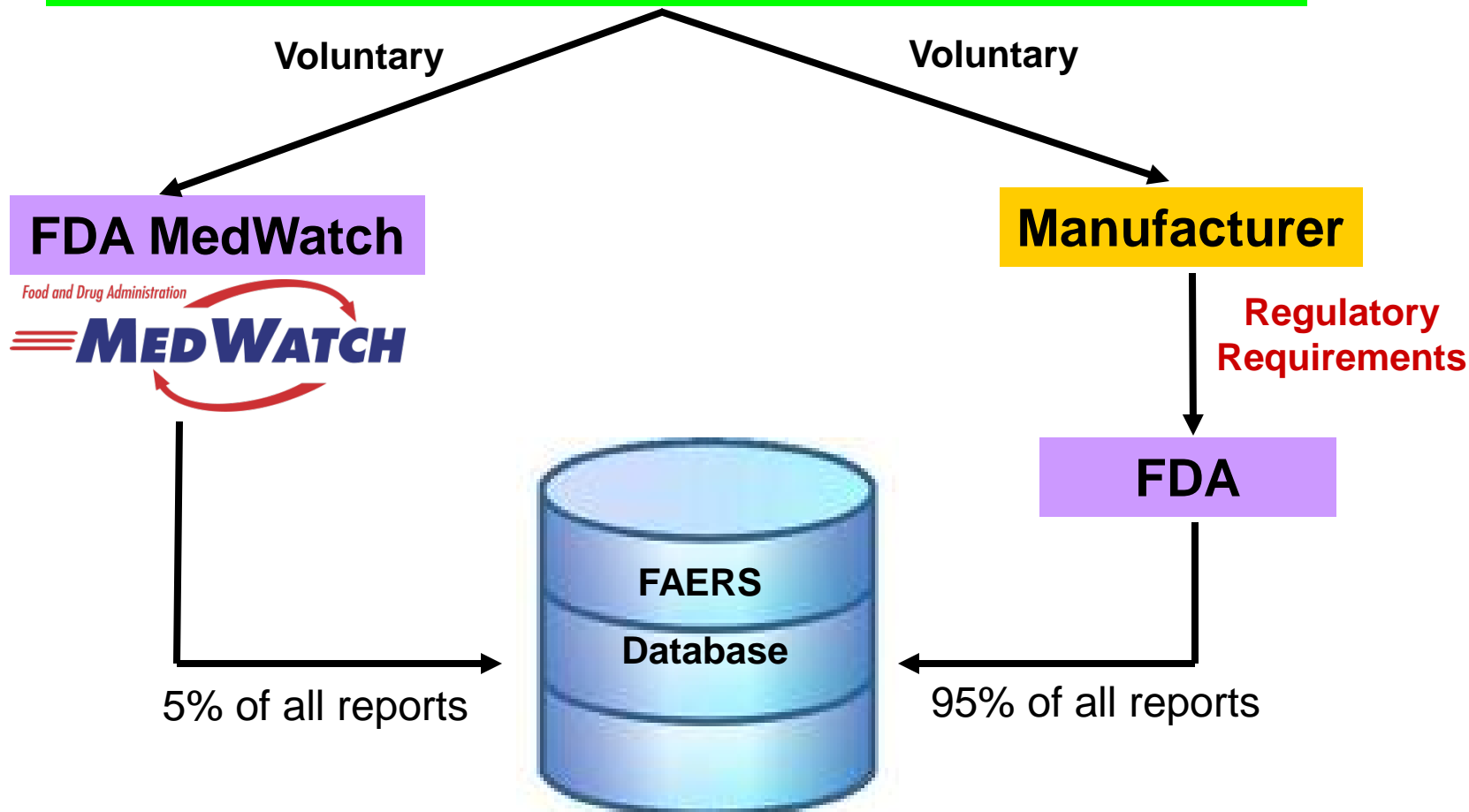
## Challenge Question #2

Which of the following countries does not require practitioners to report adverse events to a national registry?

- A. France
- B. Norway
- C. Sweden
- D. US

# How Postmarketing Reports Get to FDA

**Patients, consumer, and healthcare professionals**



# 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 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 Event

- 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

# Spontaneous Reports and FAERS



# Challenge Question #3

## True or False?

The incidence of adverse drug events can be determined through spontaneous reporting systems.

# 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

# 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

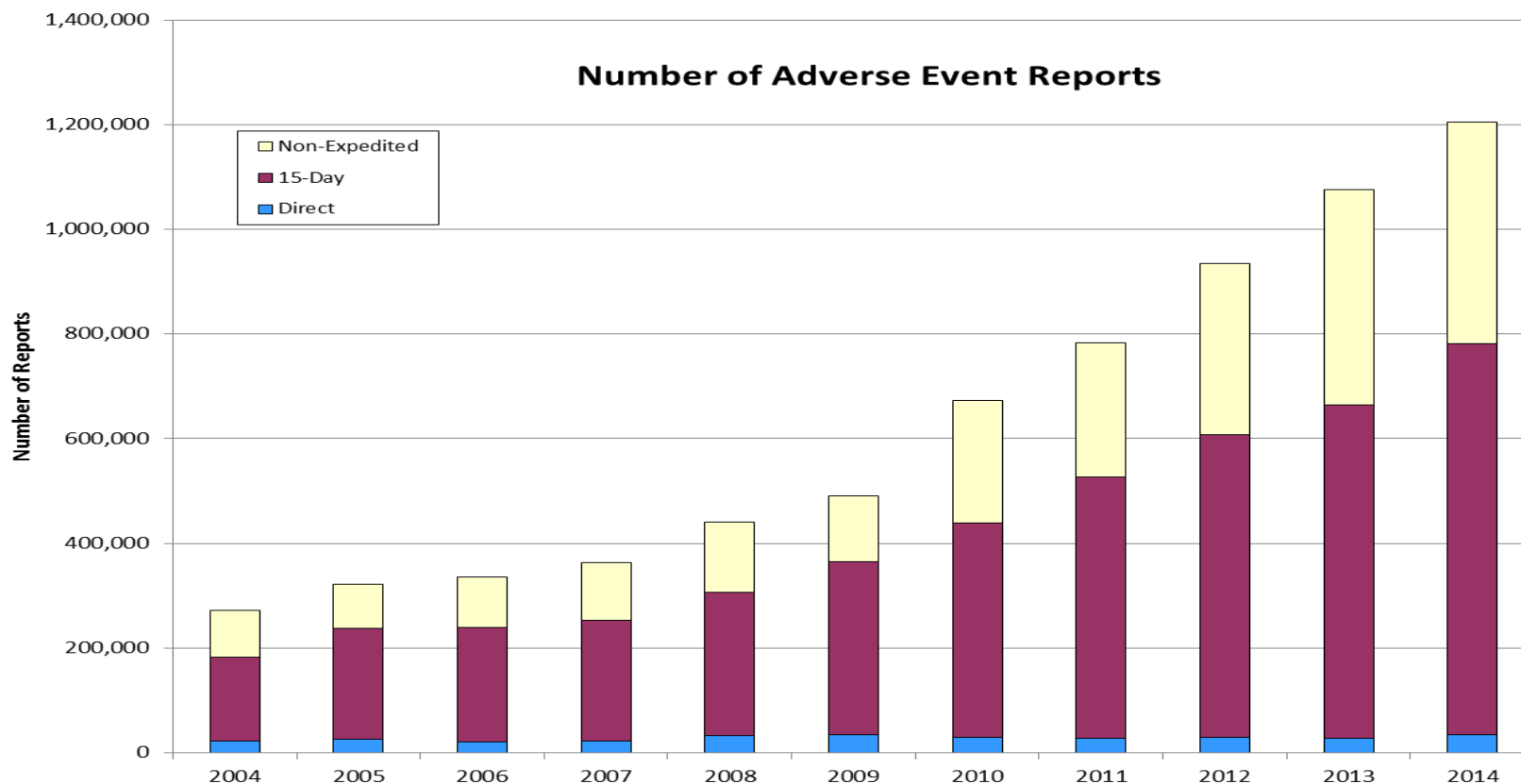


# FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 9 million reports since 1969
- Over 1.2 million new reports in 2014



# Number of Adverse Event Reports Entered into FAERS



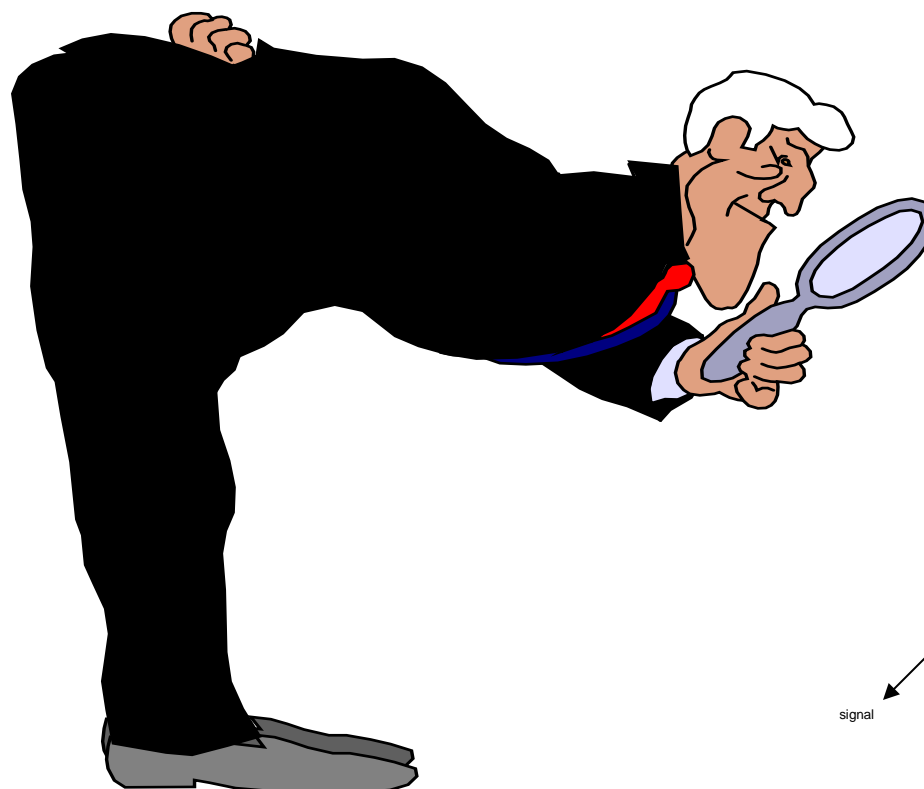
# FAERS Strengths

- Includes all U.S. marketed products
- Includes all uses
- Includes broad patient populations:
  - elderly, children, pregnant women, co-morbidities
- Especially good for events with a rare background rate
- Useful for events that occur shortly after exposure
- Detection of events not seen in clinical trials (“signal generation”)
- Identification of reporting trends, possible risk factors, at risk populations, and other clinically significant emerging safety concerns

## FAERS is less useful for:

- Events with high background rates
- Worsening of pre-existing disease
- Issue is beyond the name of the drug
- Comparative incidence rates
- Comparing drugs in the same class
- Adverse events that could also be manifestations of the disease for which the drug is indicated
- Reporting biases

# Safety Signal Detection



Did you  
see it??

signal





## Challenge Question #4

**A safety signal could be:**

- A. New, previously unknown, adverse event
- B. New drug interaction
- C. An observed change in quantity, severity or the affected populations of a known adverse event
- D. All of the above

# 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



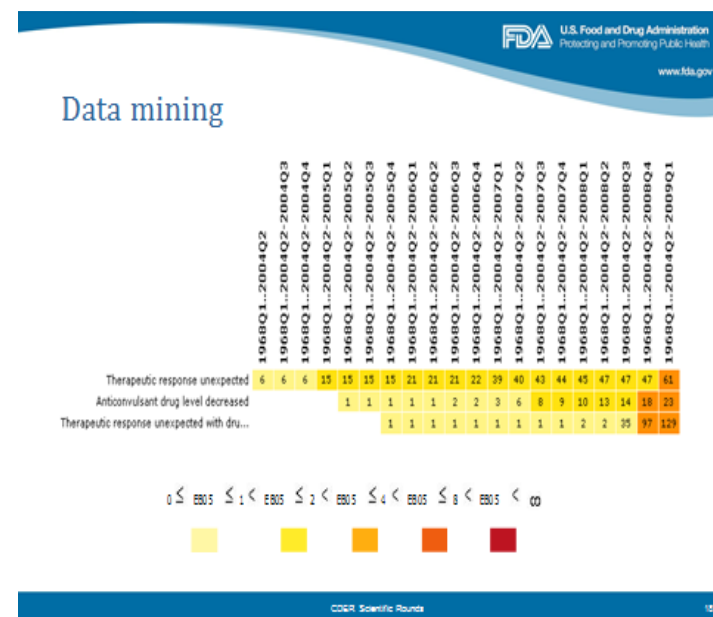
# Sources of Possible Safety Signals

- Routine pharmacovigilance
  - FAERS
  - Data mining
  - Periodic Safety Update Reports from drug manufacturers
- Study results
- Medical literature
- Media
- New Drug Application (NDA) safety database
- Outside inquiry
- Foreign Regulatory Agencies
- Others



# Use of Data Mining

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





# 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 \_\_\_\_\_

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011  
See OMB statement on reverse.

**FDA USE ONLY**  
Triage unit sequence # \_\_\_\_\_

**A. PATIENT INFORMATION**  
1. Patient Identifier # at time of event: \_\_\_\_\_  
Sex:  Female  Male  
Weight: \_\_\_\_\_ lb or \_\_\_\_\_ kg

**B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR**  
Check all that apply:  
1.  Adverse Event  Product Problem (e.g., defects/malfunctions)  
 Product Use Error  Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)  
 Death  Disability or Permanent Damage  
 Life-threatening  Congenital Anomaly/Birth Defect  
 Hospitalization - initial or prolonged  Other Serious (Important Medical Events)  
 Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) \_\_\_\_\_ 4. Date of this Report (mm/dd/yyyy) \_\_\_\_\_

5. Describe Event, Problem or Product Use Error  
\_\_\_\_\_

6. Relevant Tests/Laboratory Data, including Dates  
\_\_\_\_\_

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)  
\_\_\_\_\_

**C. PRODUCT AVAILABILITY**  
Product Available for Evaluation? (Do not send product to FDA)  
 Yes  No  Returned to Manufacturer on: \_\_\_\_\_ (mm/dd/yyyy)

**D. SUSPECT PRODUCT(S)**  
1. Name, Strength, Manufacturer (from product label)  
#1 Name: \_\_\_\_\_ Strength: \_\_\_\_\_ Manufacturer: \_\_\_\_\_  
#2 Name: \_\_\_\_\_ Strength: \_\_\_\_\_ Manufacturer: \_\_\_\_\_

2. Health Professional's Occupation  
 Yes  No

3. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:

4. Also Reported to:  
 Manufacturer  Distributor/Importer

**E. SUSPECT MEDICAL DEVICE**  
1. Brand Name \_\_\_\_\_  
2. Common Device Name \_\_\_\_\_  
3. Manufacturer Name, City and State \_\_\_\_\_  
4. Hours \_\_\_\_\_ 5. Operator of Device  
 Hospital/Physician  Lay User/Patient  
Catalog # \_\_\_\_\_ Expiration Date (mm/dd/yyyy) \_\_\_\_\_  
Serial # \_\_\_\_\_ Other # \_\_\_\_\_  
6. If Implanted, Give Date (mm/dd/yyyy) \_\_\_\_\_ 7. If Explanted, Give Date (mm/dd/yyyy) \_\_\_\_\_  
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?  
 Yes  No  
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor \_\_\_\_\_

**F. OTHER (CONCOMITANT) MEDICAL PRODUCTS**  
Product names and therapy dates (exclude treatment of event)  
\_\_\_\_\_

**G. REPORTER (See confidentiality section on back)**  
1. Name and Address  
Name: \_\_\_\_\_ Address: \_\_\_\_\_  
City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_  
Phone # \_\_\_\_\_ E-mail \_\_\_\_\_

**FORM FDA 3500 (1/09)** Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

PLEASE TYPE OR USE BLACK INK

Patient Identifier

Event or Problem

Reporter

Product

# Consumer MedWatch Form

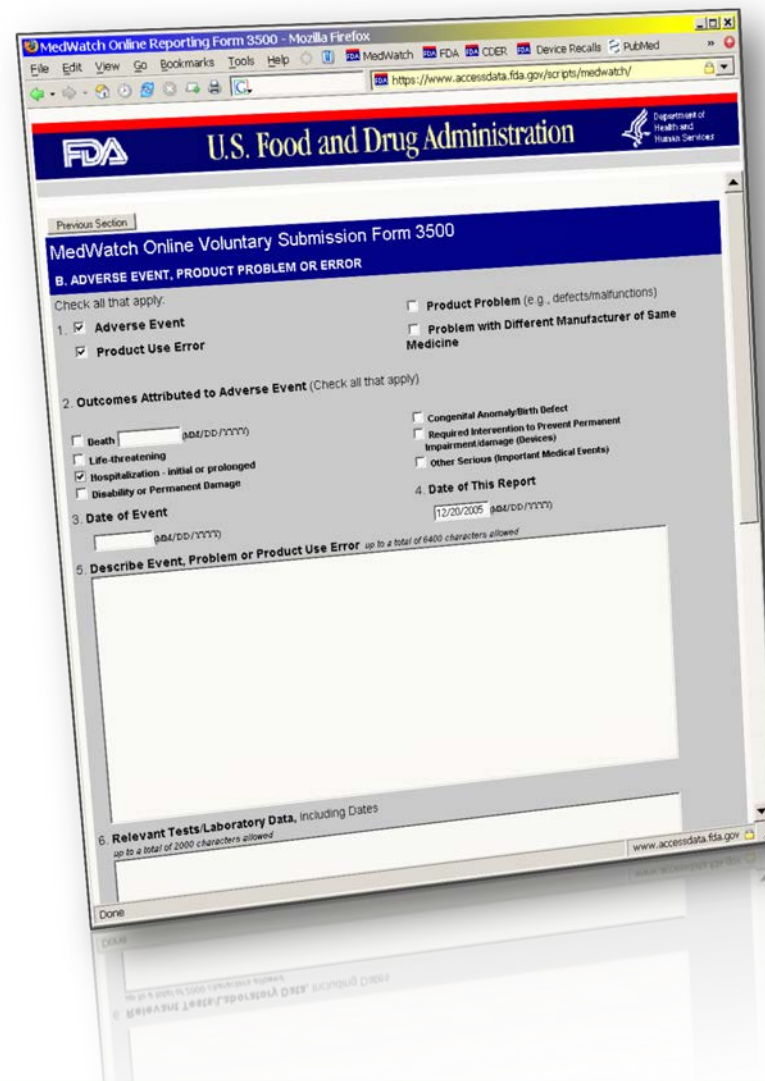
<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration</p> <p><b>MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)</b></p>	<p>Form Approved: OMB No. 0910-0291 Expiration Date: 6/30/2015 <i>(See FRA Statement on preceding general information page)</i></p>

Section A – About the Problem	
<p>What kind of problem was it? <i>(Check all that apply)</i></p> <p><input type="checkbox"/> Were hurt or had a bad side effect <i>(including new or worsening symptoms)</i></p> <p><input type="checkbox"/> Used a product incorrectly which could have or led to a problem</p> <p><input type="checkbox"/> Noticed a problem with the quality of the product</p> <p><input type="checkbox"/> Had problems after switching from one product maker to another maker</p>	<p>Did any of the following happen? <i>(Check all that apply)</i></p> <p><input type="checkbox"/> Hospitalization – admitted or stayed longer</p> <p><input type="checkbox"/> Required help to prevent permanent harm <i>(for medical devices only)</i></p> <p><input type="checkbox"/> Disability or health problem</p> <p><input type="checkbox"/> Birth defect</p> <p><input type="checkbox"/> Life-threatening</p> <p><input type="checkbox"/> Death <i>(include date):</i> _____</p> <p><input type="checkbox"/> Other serious/important medical incident <i>(Please describe below)</i></p> <p>_____</p> <p>_____</p>
<p>Date the problem occurred <i>(mm/dd/yyyy)</i></p> <p>_____</p>	<p>_____</p>
<p>Tell us what happened and how it happened. <i>(Include as many details as possible)</i></p> <p>_____</p> <p>_____</p> <p style="text-align: right;"><b>Continue to Page</b></p>	
<p>List any relevant tests or laboratory data if you know them. <i>(include dates)</i></p> <p>_____</p> <p>_____</p> <p style="text-align: right;"><b>Continue to Page</b></p>	
<p><b>For a problem with a product, including</b></p> <ul style="list-style-type: none"> <li>▪ prescription or over-the-counter medicine</li> <li>▪ biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies</li> <li>▪ nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods</li> <li>▪ cosmetics or make-up products</li> <li>▪ foods (including beverages and ingredients added to foods)</li> </ul> <p style="text-align: right;"><b>Go to Section B</b></p>	
<p><b>For a problem with a medical device, including</b></p> <ul style="list-style-type: none"> <li>▪ any health-related test, tool, or piece of equipment</li> <li>▪ health-related kits, such as glucose monitoring kits or blood pressure cuffs</li> <li>▪ implants, such as breast implants, pacemakers, or catheters</li> <li>▪ other consumer health products, such as contact lenses, hearing aids, and breast pumps</li> </ul> <p style="text-align: right;"><b>Go to Section C (Skip Section B)</b></p>	

- MedWatch Form 3500B
- Includes 4 primary components
  - Patient
  - Product
  - Event
  - Reporter
- User-friendly format for non-health care professionals



- How to Report:
  - Online  
([www.fda.gov/medwatch](http://www.fda.gov/medwatch))
  - Download the form
    - Mail
    - Fax 1-800-332-0178
- For questions about the form:  
1-800-332-1088



# 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, 2011. On an unknown date, the patient developed liver failure; additional information was not provided.



## Case #2: Best Case Representative

- 59-year-old male with type 2 diabetes, hyperlipidemia, and hypertension. No history of liver disease.
- Started Drug X on February 11, 2011.
- 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 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 Series Development and Evaluation

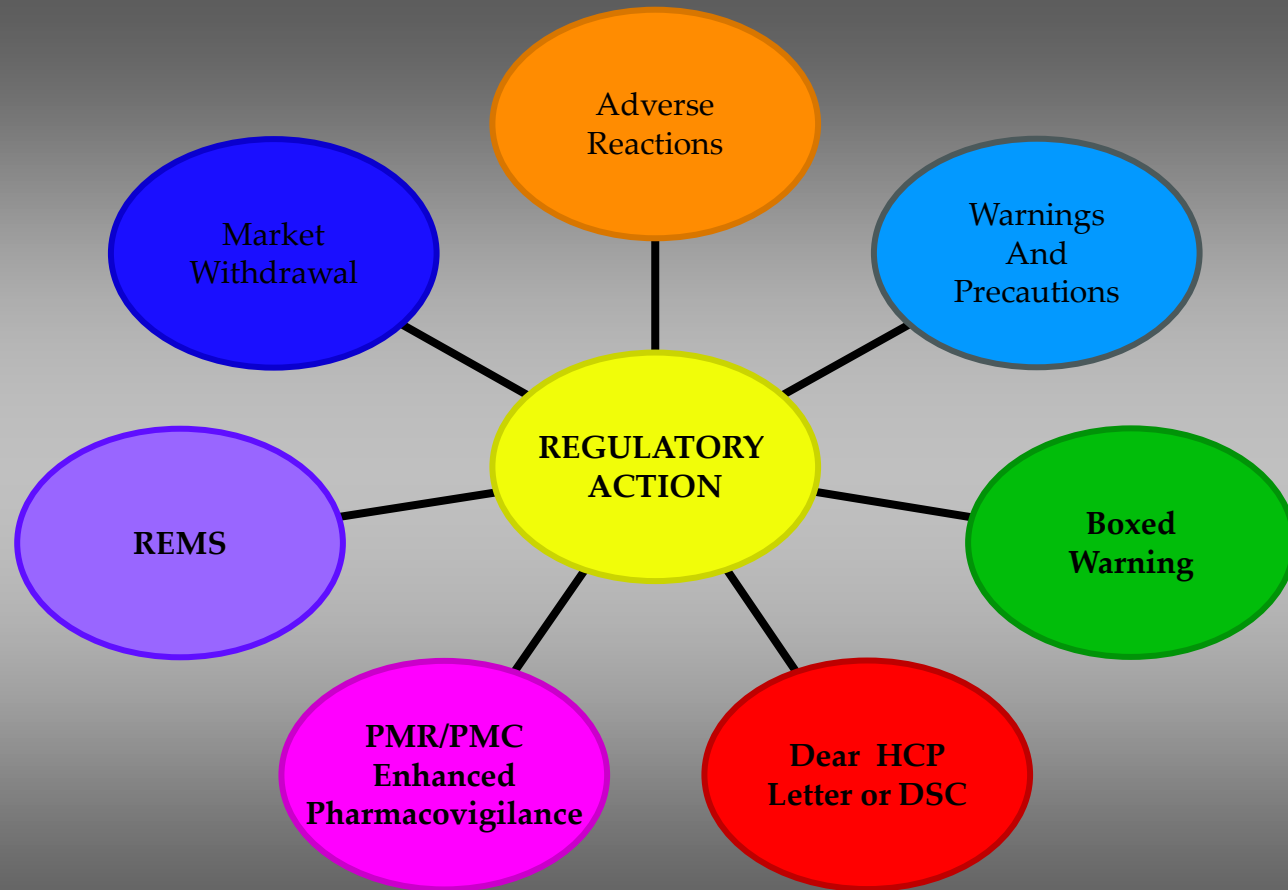
# Developing a Case Series

- Identify a well-documented case in 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.

# Principles of Case Evaluation

- Temporal relationship
- Causality assessment- World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified
- Key factors in causality assessment including, but not limited to
  - Dechallenge/rechallenge
  - Comorbidities
  - Concomitant medications
  - Consistent with pharmacological effects ( biologic plausibility)

# 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

Report a Problem

Safety Information

Stay Informed

## What's New

- [Heart Sync Inc. Multi-function Defibrillation Electrodes: Device Correction - Connector Incompatibility with Philips FR3 and FRx Defibrillator Units May result in a delay in therapy.](#) Posted 12/03/2014
- [Gel-E Donut and Squishon 2 Products by Children's Medical Ventures: Recall - Potential Mold Contamination UPDATED 12/02/2014.](#) Recall classified as Class I. Possibility of fungal infection should patients come in contact with mold. Originally posted 11/14/2014

## 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.

## Resources for You

- [2014 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 \(PDF - 1.2MB\)](#)

<http://www.fda.gov/Safety/MedWatch>



# 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- Postmarketing 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>
- Postmarketing 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

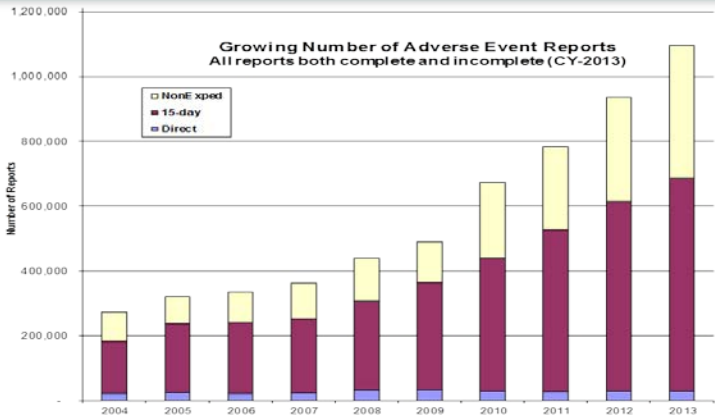
- CDER – Center for Drugs Evaluation & Research
- CFR – Code of Federal Regulations
- DEPI I & II – Division of Epidemiology I & II
- DILIN – Drug-Induced Liver Injury Network
- DMEPA – Division of Medication Error & Prevention Analysis
- DPV I & II – Division of Pharmacovigilance I & II
- DRISK – Division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

# Acronyms, cont'd

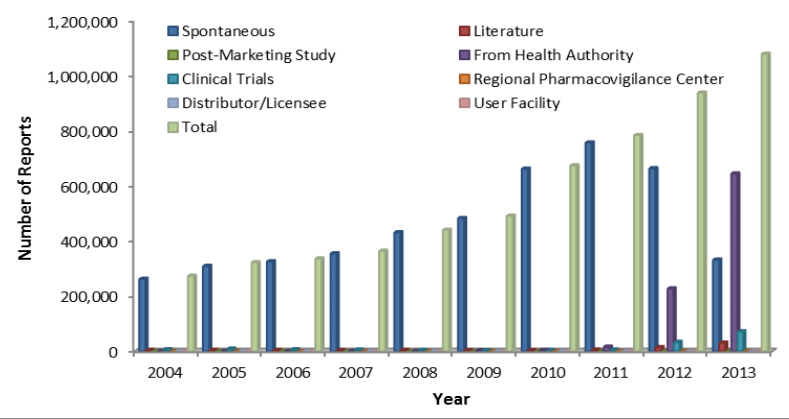
- FDAAA – Food & Drug Administration Amendment Act
- FAERS – FDA Adverse Events Reporting System
- HCP – Health Care Provider
- MO – Medical Officer
- NDA – New Drug Application
- OND – Office of New Drugs
- PMC – Postmarketing Commitment
- PMR – Postmarketing Requirement
- REMS – Risk Evaluation & Mitigation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

# FAERS Metrics

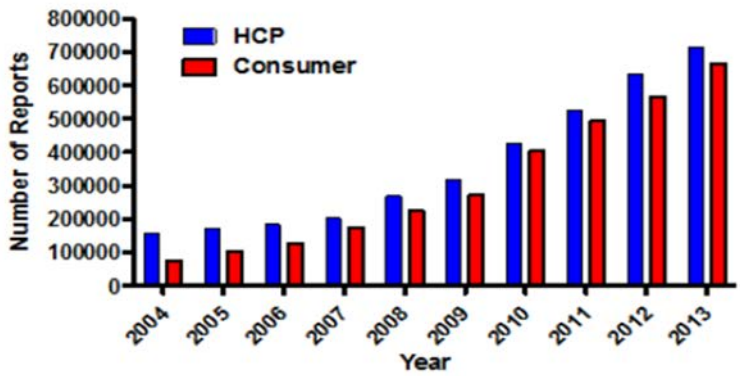
## Reports per Year



## Reports by Source Type per Year



## Reports by Reporter Type per Year



## Reports by Age Group and Gender per Year

