

Postmarket Safety Surveillance of Drugs and Therapeutic Biologics

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Center for Drug Evaluation and Research (CDER)

Food and Drug Administration (FDA)

Learning Objectives

- Understand how FDA identifies and evaluates safety issues associated with drugs and biologics
- Increase awareness of actions FDA takes to investigate safety issues to help manage risk
- Identify resources to learn more or educate others on FDA's evolving role in drug safety

Outline

- Background on FDA safety monitoring
- Identifying drug safety issues
- Investigating safety
- Characterizing risk
- Resources
- Questions

Background

- FDA monitors the safety of human and veterinary drugs, biologics, medical devices, foods, cosmetics, & other products
- Each Center monitors their regulated products
 - Example: Center for Devices and Radiologic Health
- Center for Drug Evaluation and Research (CDER)
 - Regulates prescription drugs (including biologics and generics, and “over the counter” products
 - OSE monitors the safety of these products

Office of Surveillance & Epidemiology Organization

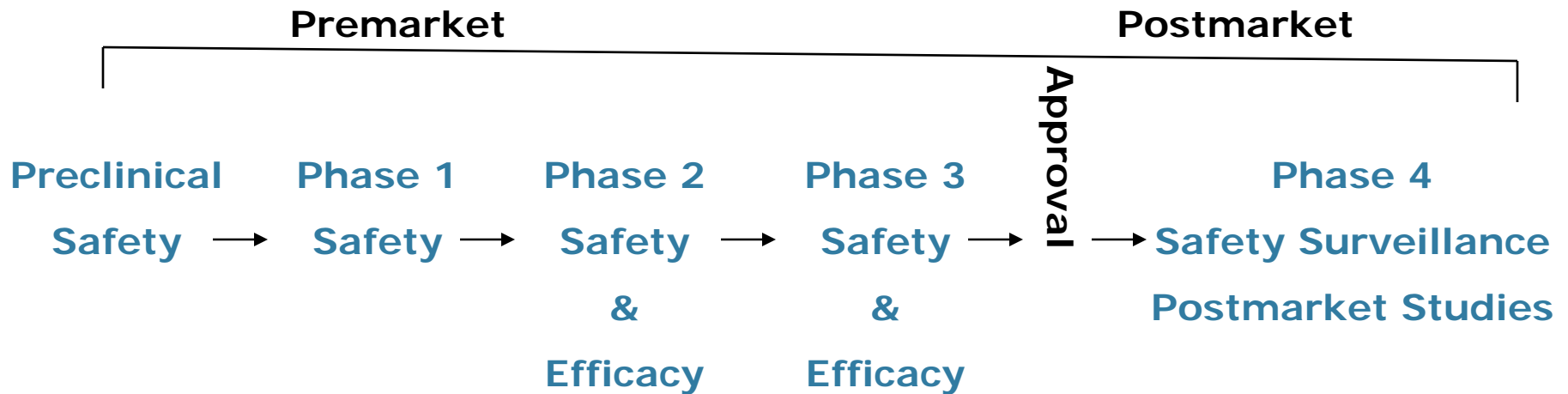
■ OSE Immediate Office

- Division of Pharmacovigilance 1 (DPV 1)
- Division of Pharmacovigilance 2 (DPV 2)
- Division of Epidemiology (DEPI)
- Division of Risk Management (DRISK)
- Division of Medication Error Prevention and Analysis (DMEPA)

Identifying Potential Safety Issues

OSE Monitors Safety Throughout the Lifecycle of Drug Products

Safety in the Lifecycle of FDA Regulated Products



Why Monitor Drug Safety Signals Following Approval?

- Limitations of premarket trials
 - Size of patient population studied
 - Narrow population studied (specific groups [children, elders] may be excluded)
 - Narrow indications studied (exclusion of certain disease states)
 - Short duration of use (not reflective of a drug's chronic use)
- Also
 - Drug-drug/food interactions
 - Increased severity or frequency of known reactions
 - Potential for new “at-risk” population

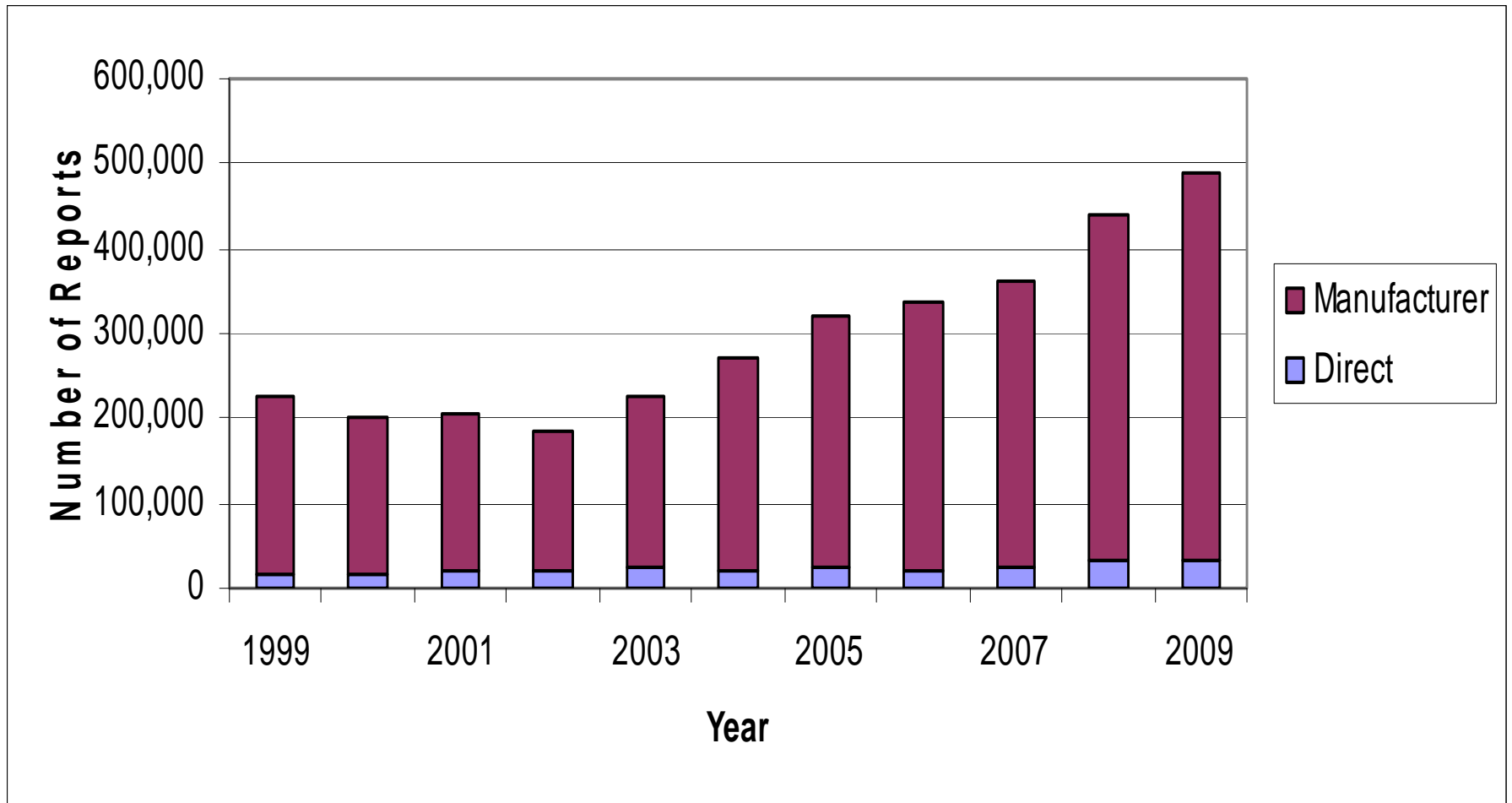
Sources of Safety Signals

- Preclinical and clinical trial data
- Postmarket surveillance studies
- Published literature
- Other regulatory agencies
- Pharmaceutical companies
- External healthcare databases
- Epidemiologic analyses
- Internet
- Spontaneous reports

Spontaneous Reports

- Adverse events reported voluntarily by consumers/patients, healthcare providers, others once on the market
- Submitted to FDA via Medwatch
 - Direct to FDA (< 10%)
 - Manufacturers (mandatory reporting)
- Reports captured in FDA's Adverse Event Reporting System (AERS)

Reports Received and Entered into AERS, 1999-2009



AERS

- Database for capturing spontaneous reports originated in 1969
- Received reports are coded using a standardized medical dictionary (MedDRA)
- Reports reviewed by OSE safety analysts
- Can query or data mine AERS to identify signals or trends

AERS

Strengths

- Provides ongoing large-scale surveillance in “real world”
- Relatively inexpensive
- Detection of rare, short latency events
- Clinician contribution
- Includes all US marketed products (Rx and OTC)

AERS

Limitations

- Underreporting
- Duplicate reporting
- Variable reporting quality (lack information)
- Spontaneous report numbers cannot be used to determine incidence of adverse events
- Difficult to attribute events with high background rate, long latency
- Reporting biases

Factors Affecting Reporting

- Nature of the adverse event
- Type of drug product and indication
- Length of time on market
- Media attention
- Extent and quality of manufacturer's surveillance system

Evaluating Safety Signals

Which Signals?

- Focus on
 - Previously unrecognized (unlabeled) safety issue
 - Change in frequency or severity
 - New risk group
 - Serious events (death, hospitalization, life-threatening, disability, congenital anomaly, or required intervention)
- Look for patterns, but one well documented report may be viewed as a signal
- Signals require careful evaluation to exclude other causes or biases

Signal Evaluation

- 1) Develop case series
 - Determine AERS search criteria
 - Define case definition and case selection
- 2) Search other sources for additional reports/information
- 3) Perform case level (“hands on”) review
- 4) Summarize case descriptive information
- 5) Case series analysis

Analysis

- Consider
 - Temporal relationship (exposure time to event)
 - Plausibility
 - Concurrent medications and co-morbidities
 - Positive dechallenge or rechallenge
 - Event identified in clinical trials
 - Absence of alternative explanations
 - Background rates and drug use
- Engage relevant scientific experts
- Decision/Recommendations

Possible Recommendations

- Labeling revisions or other regulatory action (market withdrawal)
- FDA communication (targeted or widespread)
 - healthcare provider or patient information sheets, public health advisory, early communications
- Continue to monitor adverse event of interest
- Risk evaluation plans (DEPI)
 - Specific pharmacovigilance plans (enhanced surveillance, studies, registries)
- Risk management plans (REMS)

Characterizing Drug Safety Risks Division of Epidemiology

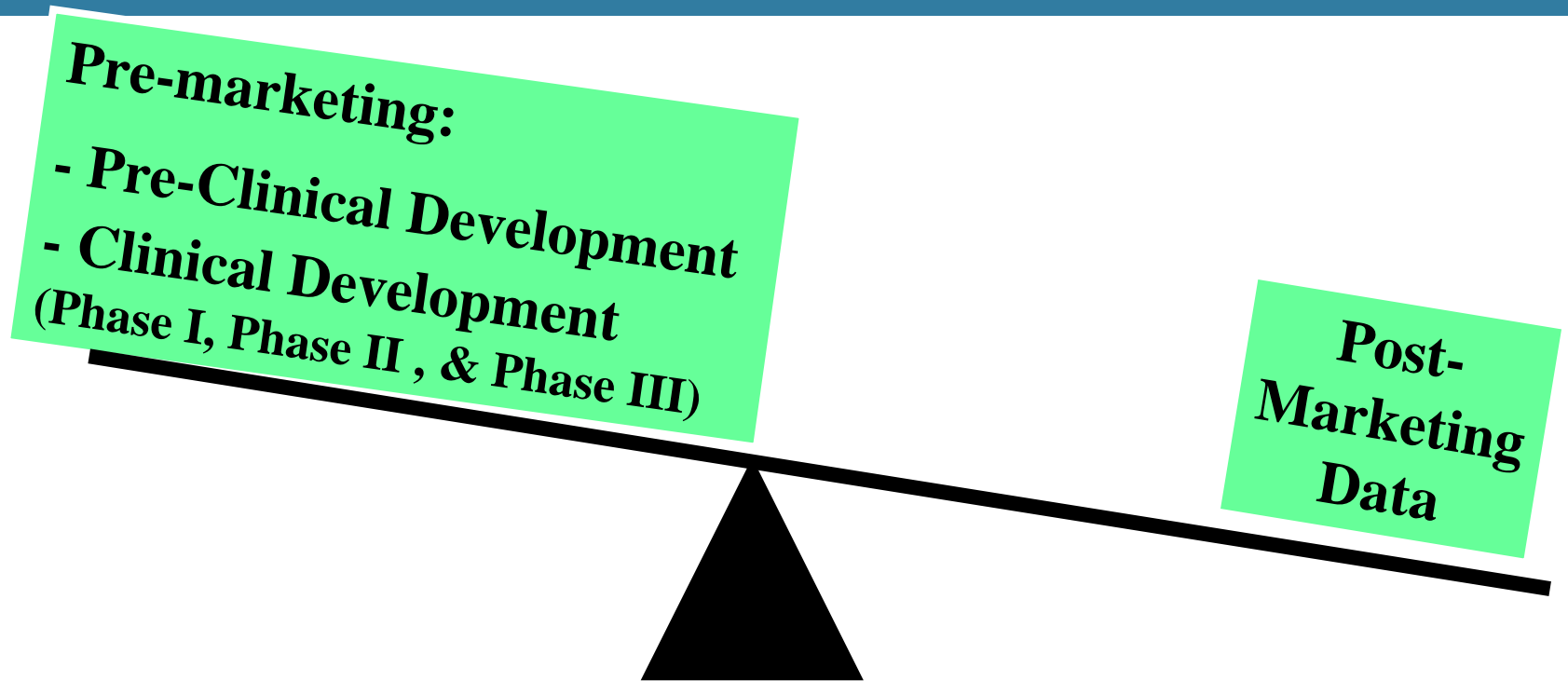
Where do we get more data about drug safety?

Pre-marketing:

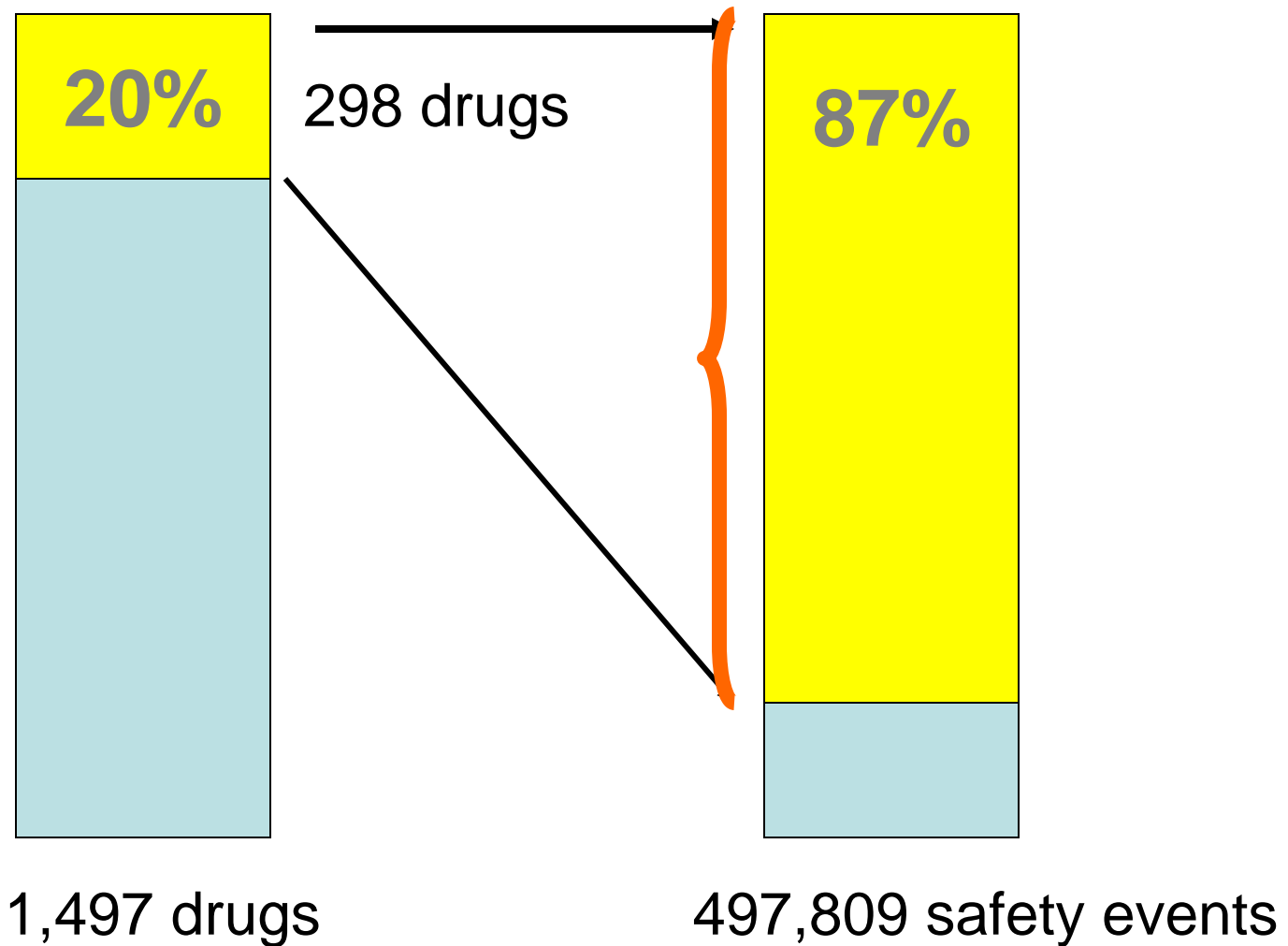
- Pre-Clinical Development
- Clinical Development (Phase I, Phase II , & Phase III)

Post-Marketing Data

Where we get more data about drug safety



All drugs are NOT created equal!



What is the Drug's Safety Risk?

A Zen garden in Kyoto, Japan, contains 15 large stones surrounded by gravel. Monks meditate on the fact that one can not see all 15 stones from any one point; no matter where you sit, at least 1 stone is blocked by another



DEPI Core Functions

Characterizing Drug Risks

- 1. Epidemiologic Reviews**
- 2. Regulatory Research Program**
- 3. Drug Utilization Procurement and Analysis**

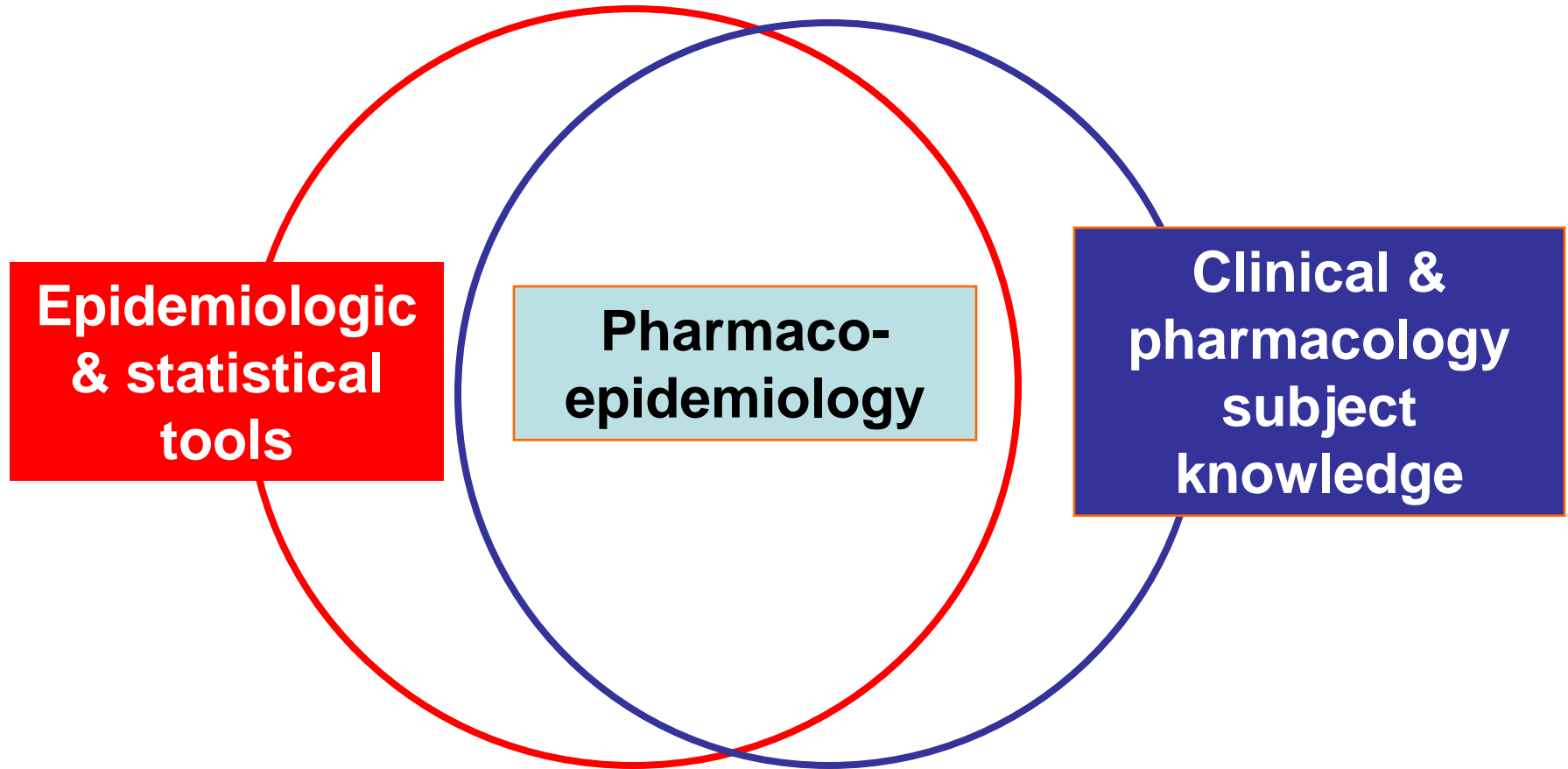
Key Questions

Pharmacoepidemiology

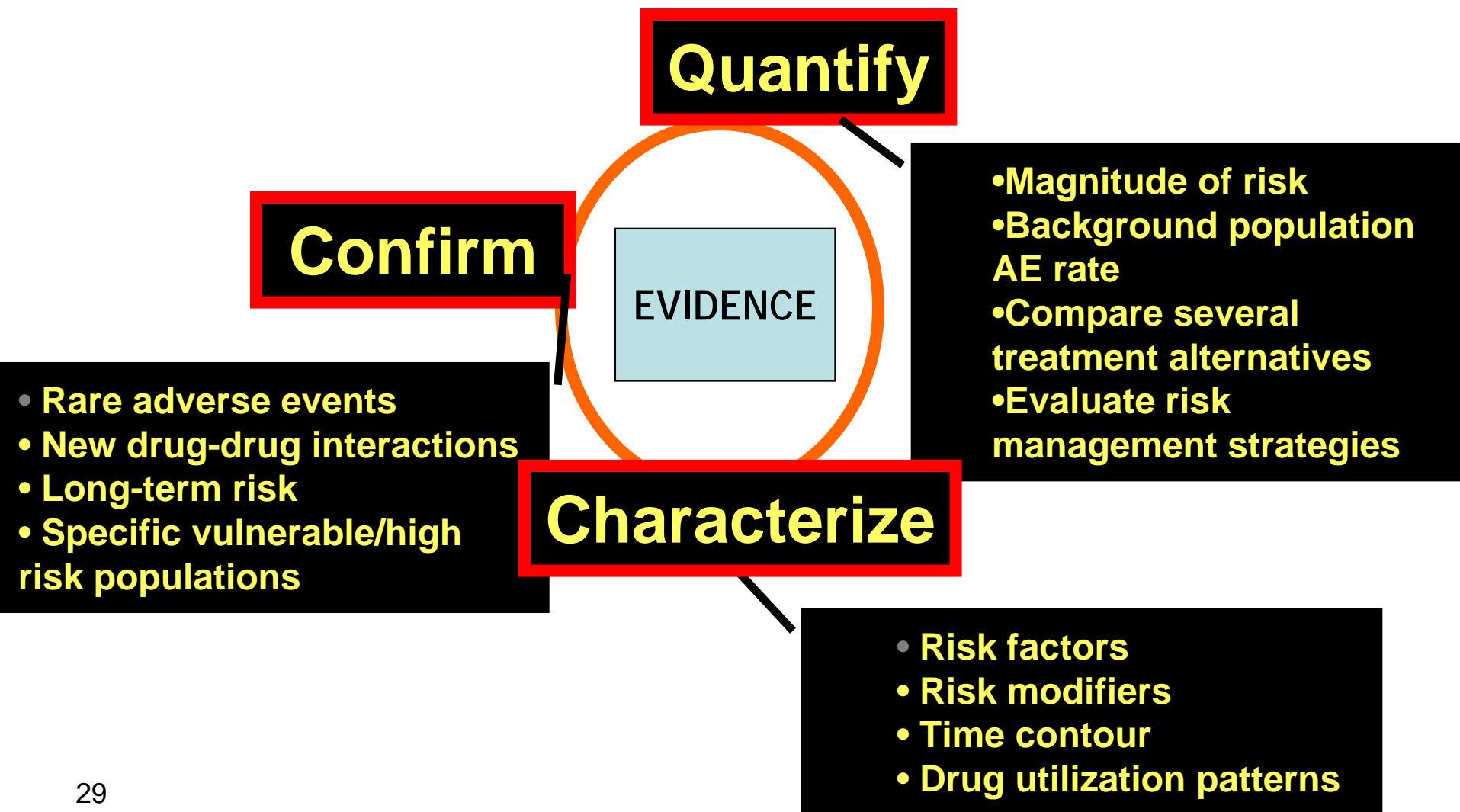
Detective Work

1. Where can a safety signal be studied?
(clinical trials, electronic medical records, or claims databases)
2. How can it be studied?
(Strategy)
3. Will a given study REALLY provide an answer?
(Methodological issues - epidemiological studies of drug effects in populations)

Components of Pharmacoepidemiology



Post-marketing Epidemiologic Studies of Drugs



Extramural Epidemiology Studies Resources

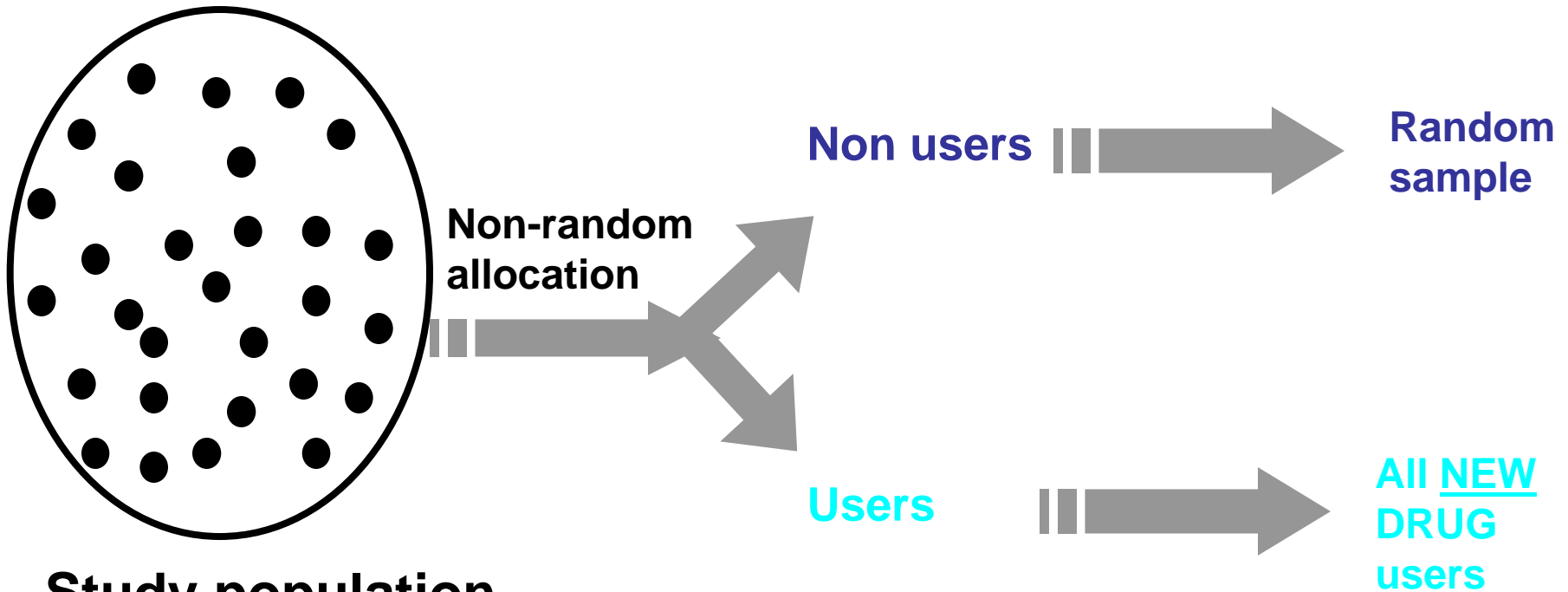
■ **Epidemiology contracts**

- Kaiser California
- Harvard Pilgrim Health Care (HMO-RN)
- Harvard Brigham and Women's (indigent elderly popn + British Columbia)
- Vanderbilt (TN + Wash. Medicaid)
- UPenn (Ontario + Quebec)

■ **Federal Collaborations**

- Department of Defense
- Veterans Administration
- Centers for Medicare and Medicaid Services
- Agency for Healthcare Research and Quality
- Centers for Disease Control and Prevention

Study Population

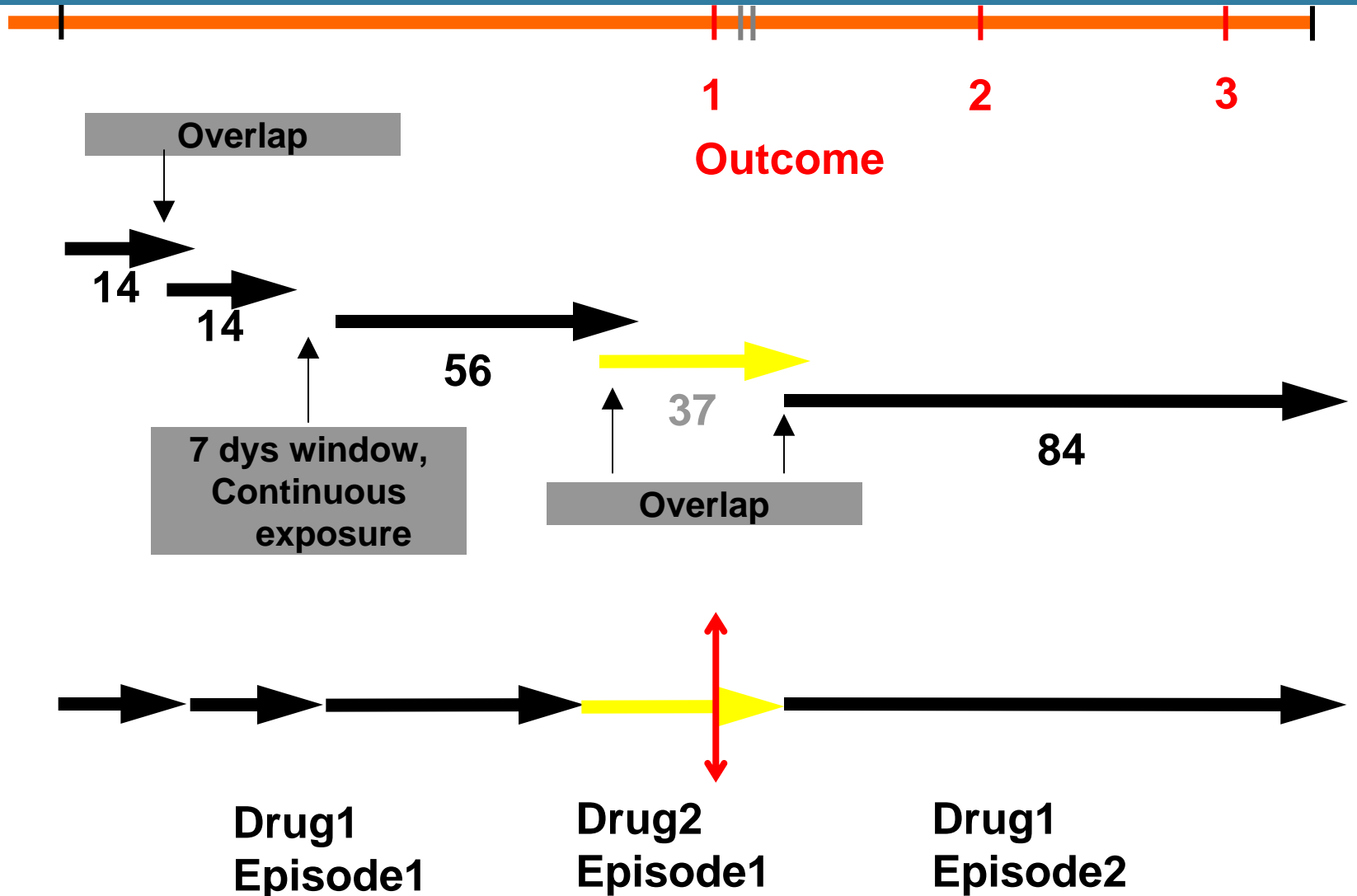


**Study population
sampled during
pre-specified
slices of time**

Construct Drug Exposure Episodes of Time

Cohort entry

End of Study

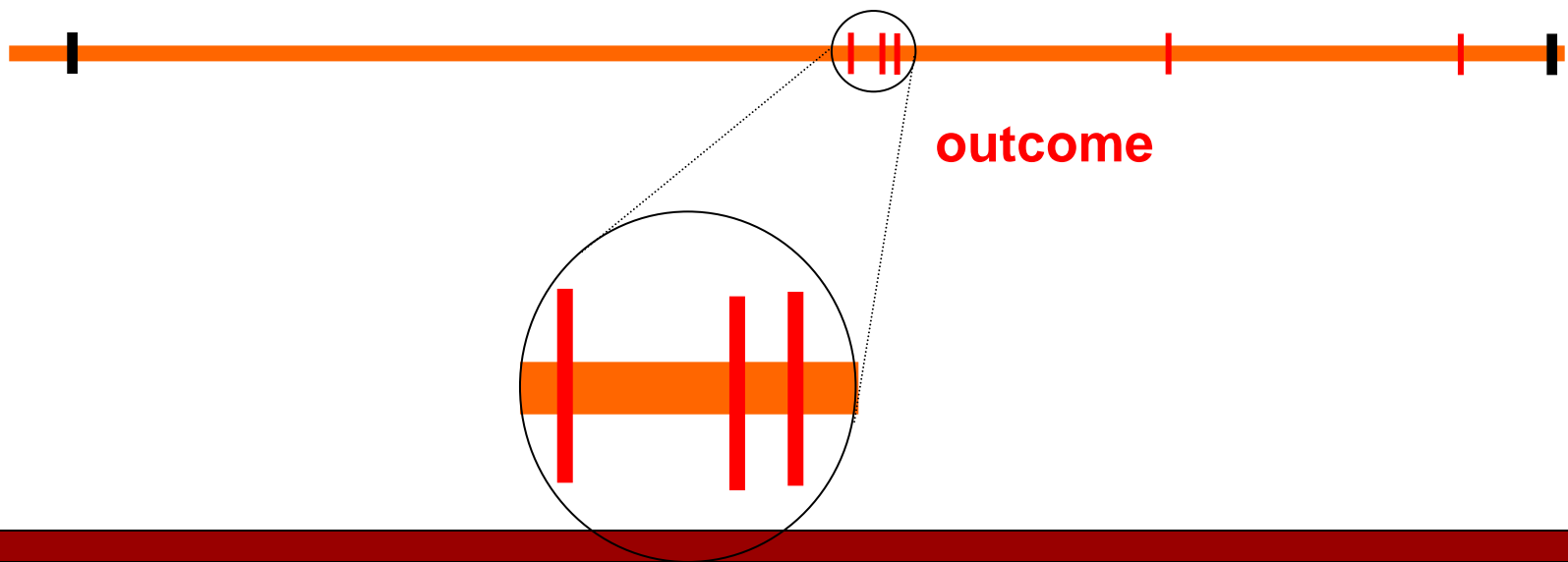


Safety "Case" Identification

- Search for cases and for relevant clinical elements consistent with adverse events
- Identify medical diagnostic codes
- Handling multiple outcomes

Cohort entry

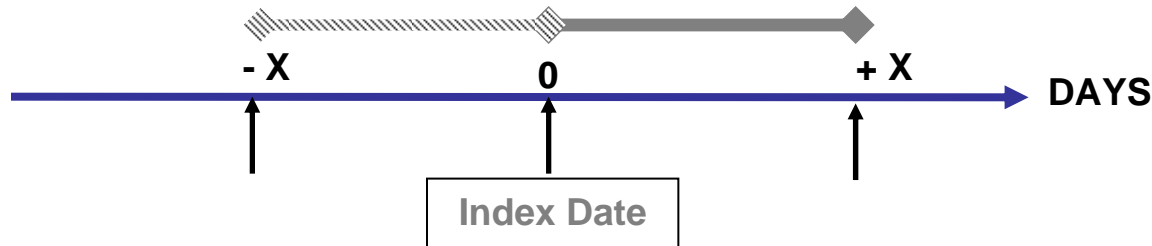
End of Study



Case Validation

■ Verification

- Review patient profile
- Use relevant clinical events, e.g. with MI look for chest pain, cardiac enzymes, etc.



■ Cross-Validation to confirm

- “Free-text” notes
- Questionnaires

Limitations & Challenges Observational Studies

- **Reference dates for comparison of rates**
 - Many factors affecting use, e.g. other media activities, generic drugs availability, promotional spending...etc
 - No measure for the lag time between a given action and its effect
 - Difficult to distinguish between the actions closely related
- **General issues**
 - Ecologic analyses
 - Use of prescription dispensing records
 - No information on indication for use
 - No means to assess “appropriateness” of use

Examples of Additional Data Sources – Including Drug Use

- IMS Health National Sales Perspectives
- IMS Combined and Integrated Promotional Services
- Verispan's VONA
- Verispan's Total Patient Tracker
 - Prescriptions dispensed in the U.S. during study period by pre-defined age group
- Census data
 - Monthly US postcensal resident population by single year of age

Increasing Drug Safety Role and Authority of FDA in Drug Risk Assessment and Management

Implementation of Title IX (Drug Safety) of The Food And
Drug Administration Amendments Act of 2007
(Took effect Sept. 27, 2007 and March 25, 2008, 180
days after enactment)

Enhanced Emphasis of FDA on Safety

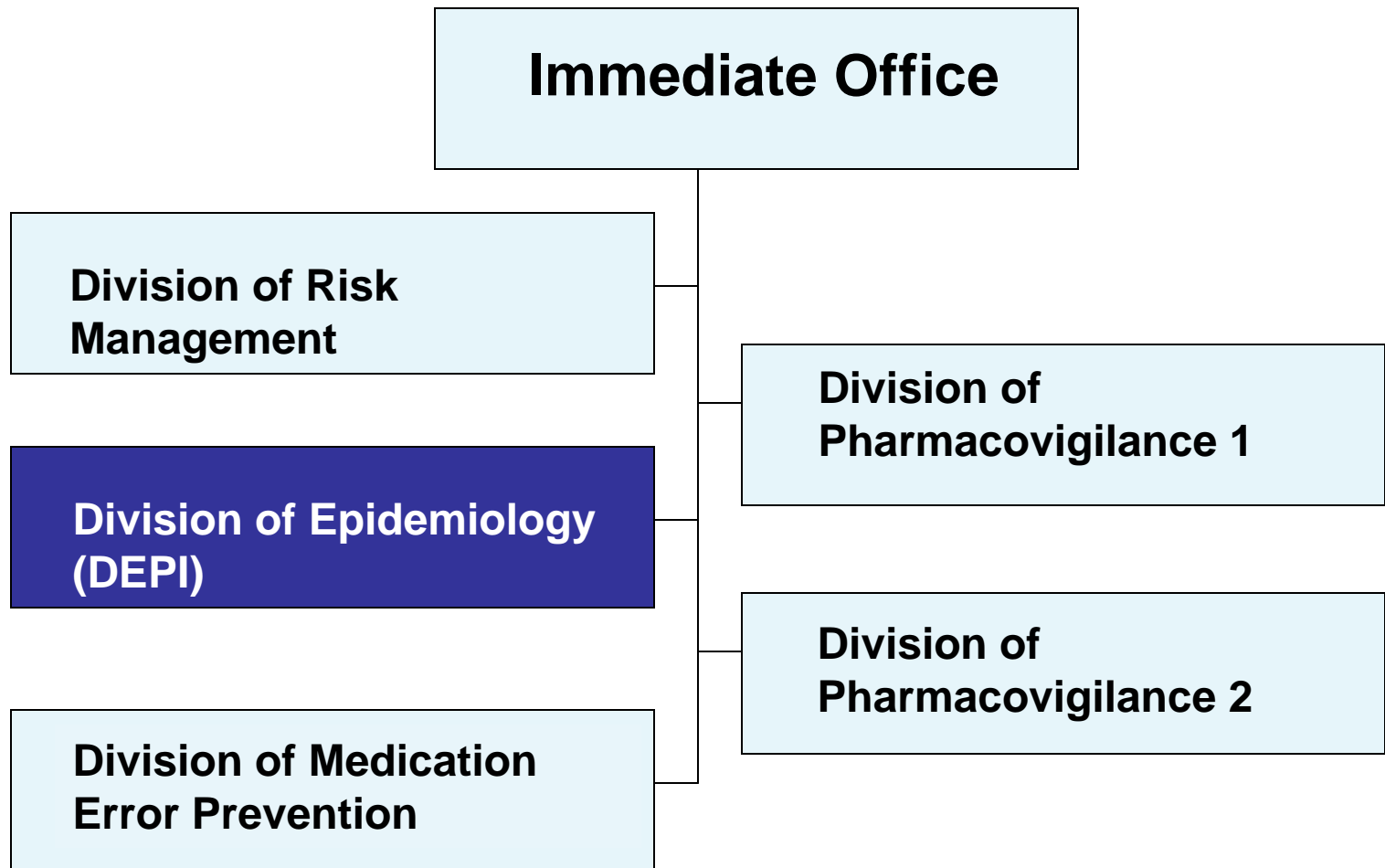
- New regulatory authorities to:
 - Require post-marketing studies and clinical trials (when certain conditions are met)
 - At the time of approval, OR
 - After approval, if new safety information becomes available
 - Before requiring a clinical trial, must determine that a post approval study or studies will not be sufficient

Changes in FDA - Expansion of Office of Surveillance & Epidemiology

- Transformation and expansion of the Office of Surveillance and Epidemiology is ongoing
 - Increase in scientists
 - Expanded use of external data for epidemiologic studies
 - Studying options for active drug safety surveillance

Office of Surveillance and Epidemiology

Evolving New Structure as of January 2008



FDA Resources

- Drug safety and availability
<http://www.fda.gov/Drugs/DrugSafety/default.htm>
- Medwatch
<http://www.fda.gov/Safety/MedWatch/default.htm>
- AERS data
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>
- Office of Surveillance and Epidemiology
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106491.htm>
- Center for Drug Evaluation and Research (CDER) home page
<http://www.fda.gov/Drugs/default.htm>

Summary

- Safety issues may arise throughout product life cycle
- FDA monitors numerous data streams (such as spontaneous reports) to identify safety signals
- FDA can characterize or study risks associated with products
- Analysis of safety issues and risks may lead to regulatory changes