Postmarket Drug Safety at the US FDA

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Pharmacovigilance and Risk Management Conferences
New Approaches, Tools and Technologies
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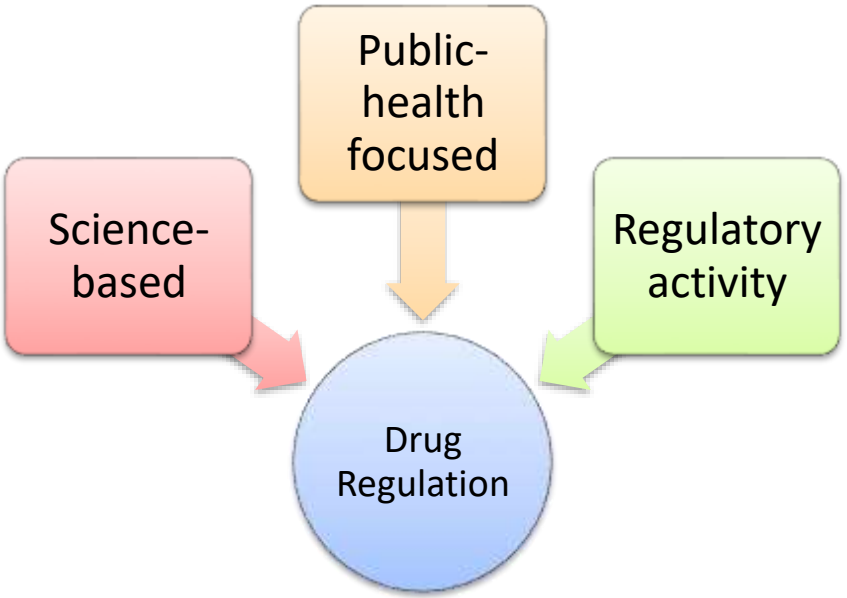
No conflicts of interest to disclose

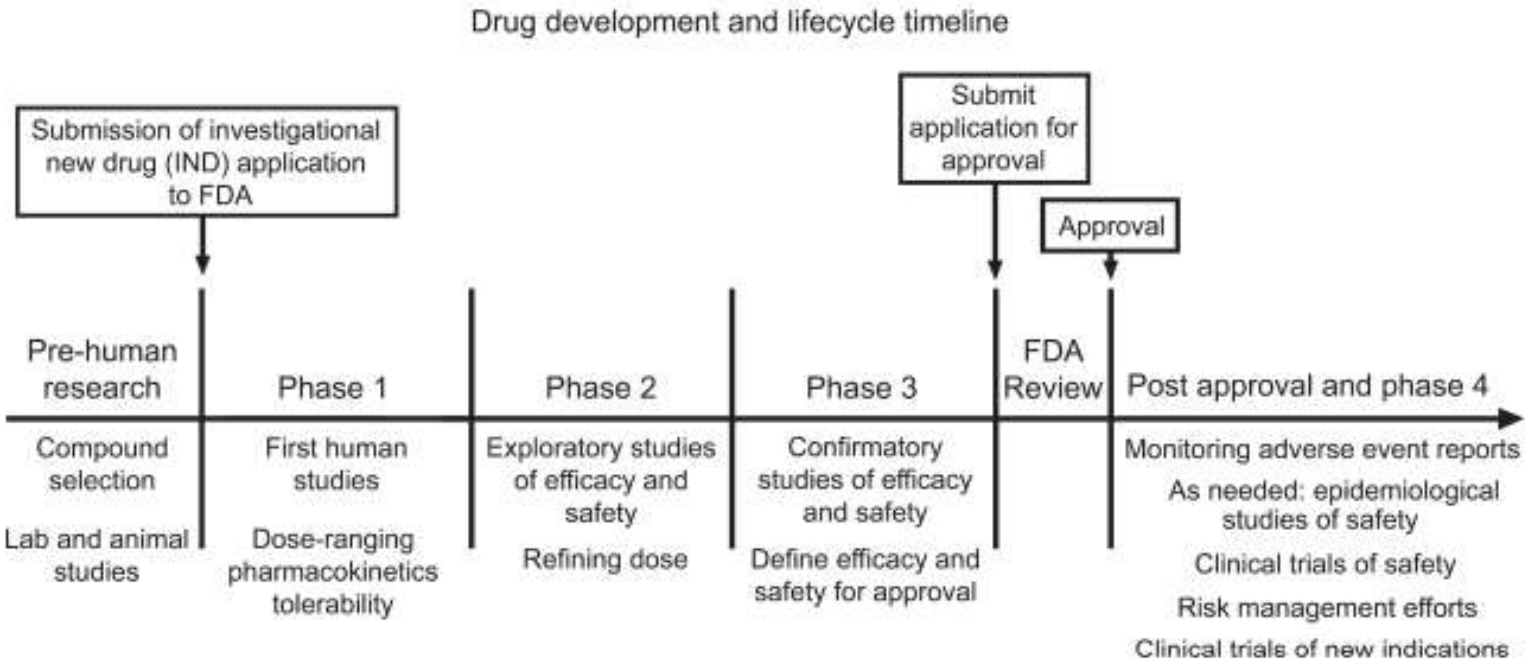
Role of the Drug Regulator

- Access to medicines
  - Assess efficacy, safety, quality
- Protection of the public
  - During clinical trials
  - Postapproval
- Information to the public



Drug Lifecycle

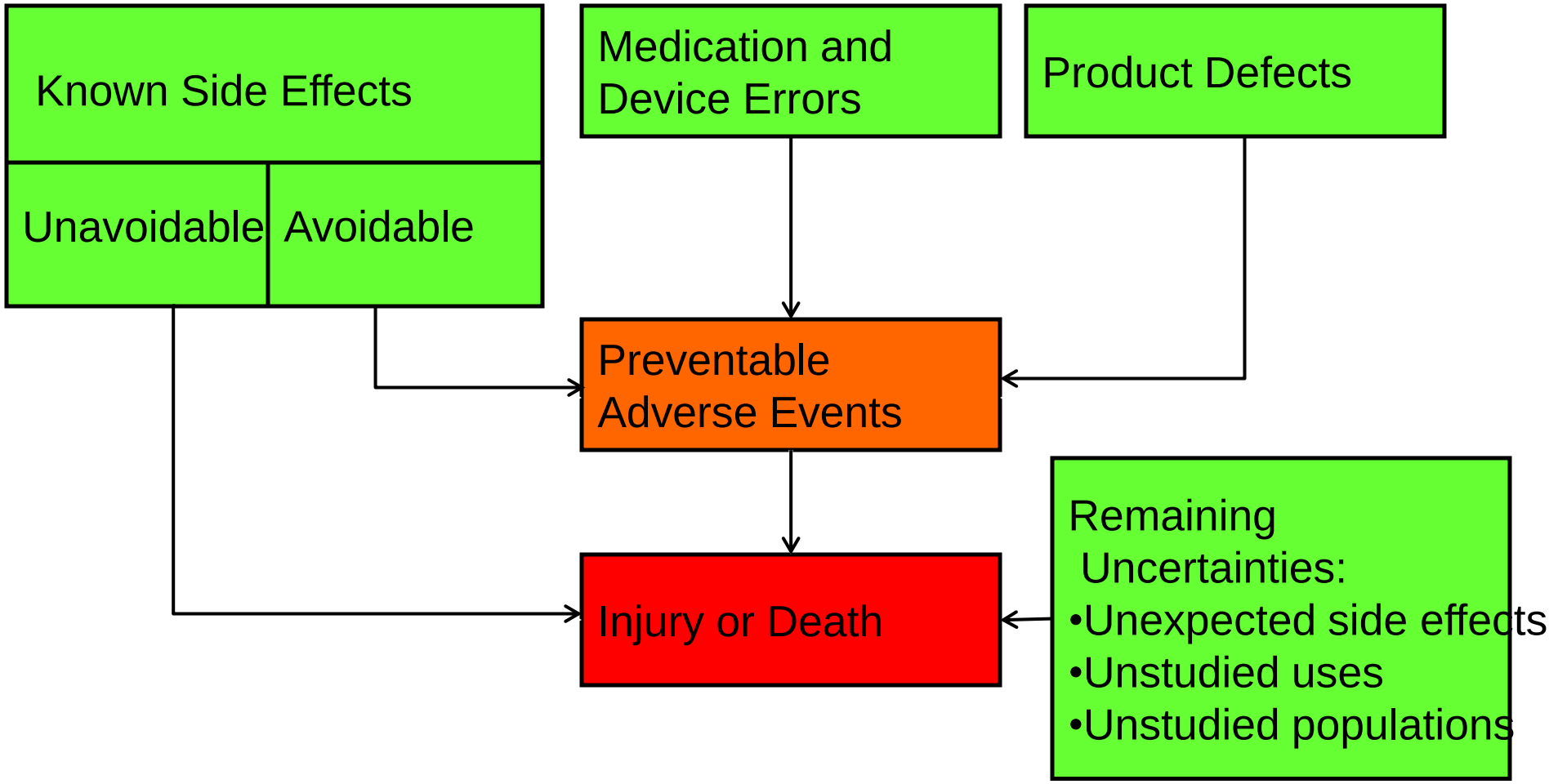
Figure **Drug development and lifecycle timeline**



The figure illustrates the principal activities that occur during the lifecycle of a drug, from prehuman studies through postmarketing surveillance. The duration of each phase varies from drug to drug and is not reflected in the figure. FDA = US Food and Drug Administration.

Source: Dal Pan GJ. The US Food and Drug Administration, neurologists, and drug development and regulation. Neurology Clinical Practice 2015;5:338-343.

Sources of Risk From Medical Products



What We Want to Learn

OSE's Four Areas of Focus

Pharmacovigilance

- Individual case safety reporting

Pharmacoepidemiology

- Population-based studies

Medication Error Prevention

- Building safety into a product

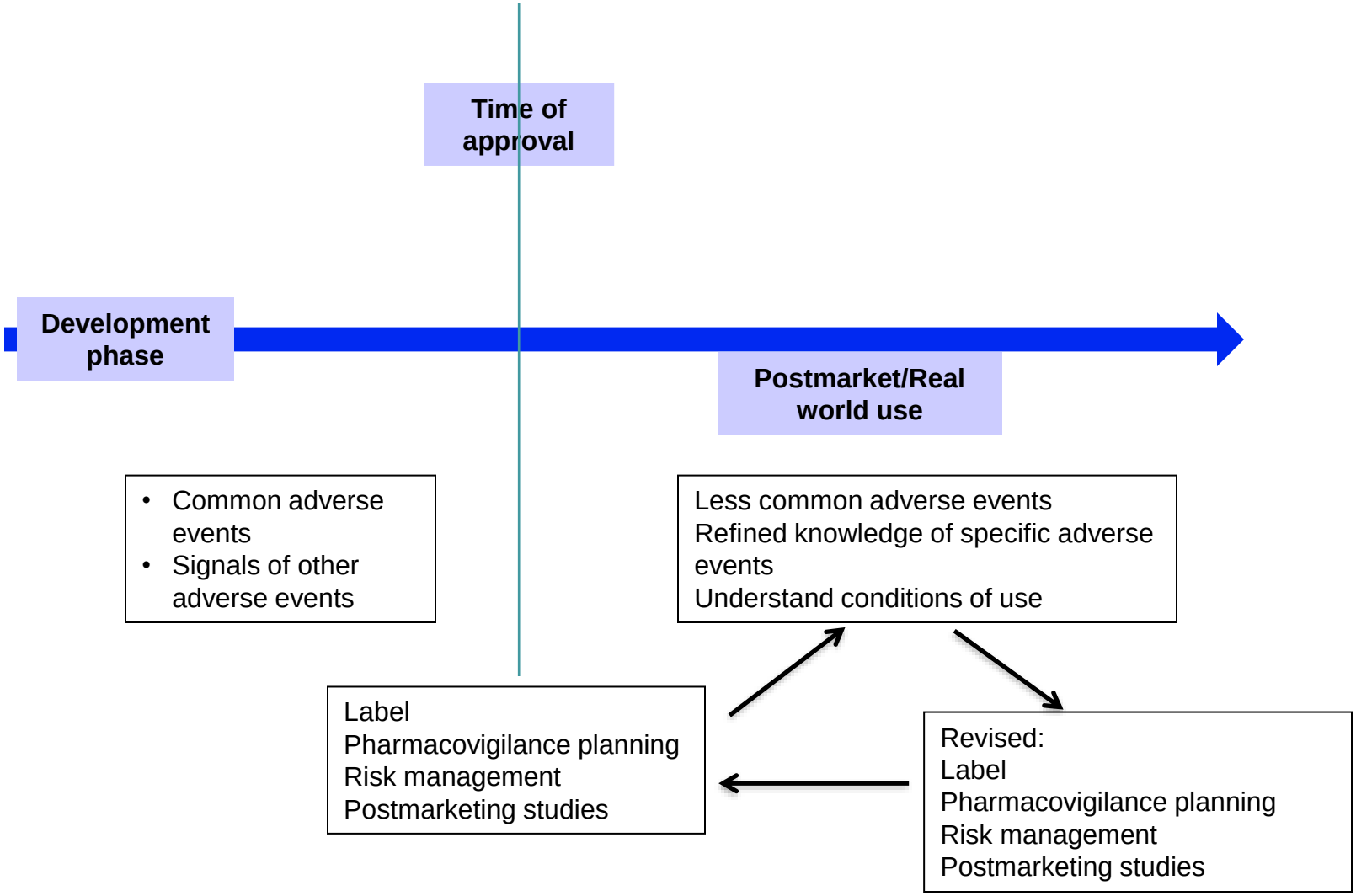
Risk Management

- Risk Evaluation and mitigation strategies

Featured Topics for This Conference

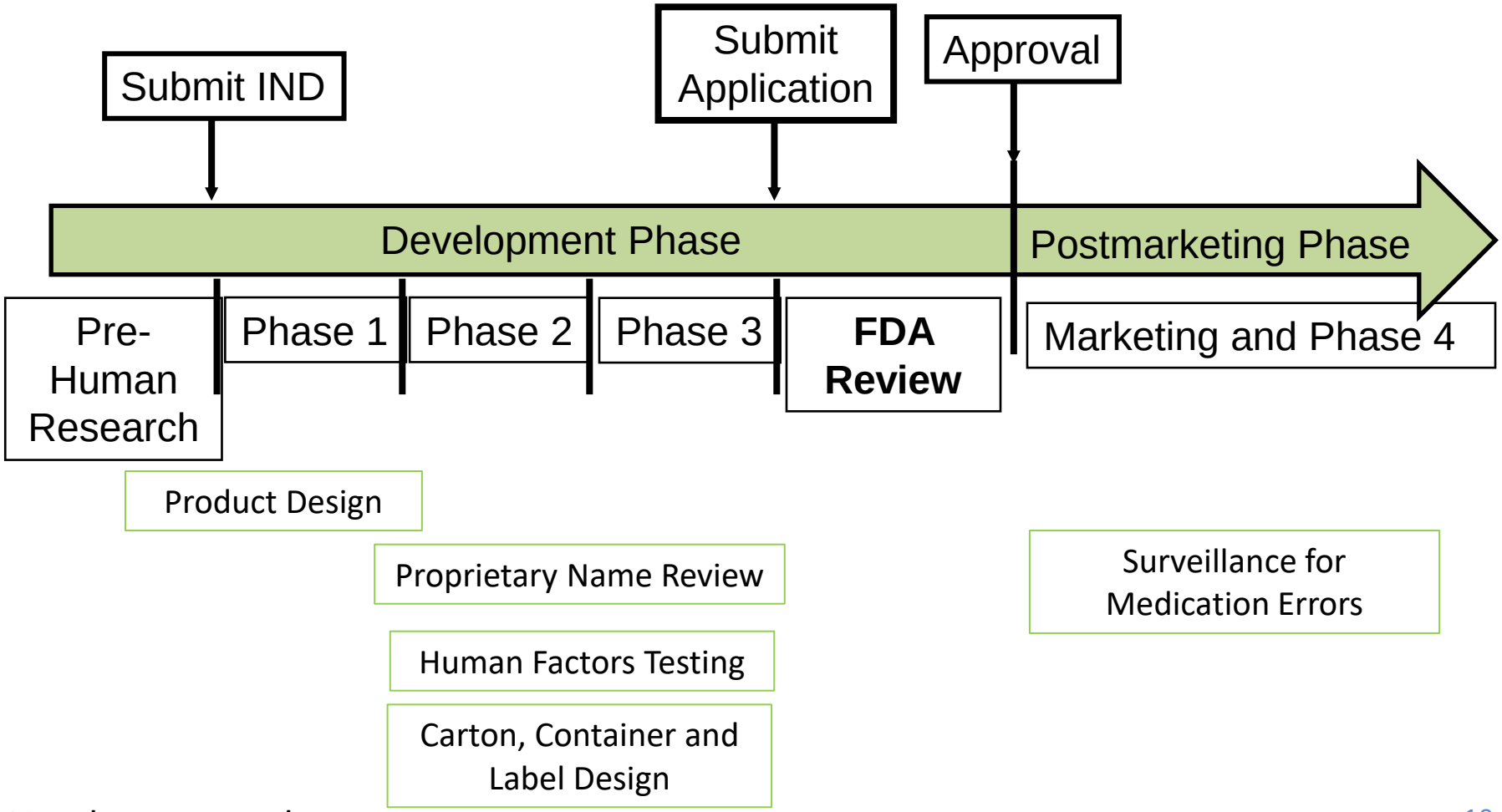
- Process for Reviewing Nonproprietary Name Suffix for Biological Products
- Best Practices for Proprietary Name(PN) Design
- Preventing Medication Errors: Designing User Interfaces to Prevent Medication Errors
- Preventing Medication Errors: Lessons Learned from Postmarket Safety Surveillance
- Division of Risk Management: Overview of Review Activities
- REMS Integration Initiatives
- Development of Shared System REMS and Implications of the Appropriations Act
- Considerations for REMS Surveys and Assessments: Planning and Reporting
- FAERS Overview
- IND Digital Reporting Overview
- Combination Products: Reporting Device Information and Malfunctions
- ICSR Data Quality of Coding - Products, Adverse Events and Medication Errors
- Postmarket Safety Surveillance
- FDA's Sentinel Initiative

Lifecycle of drug safety knowledge



This process is iterative and incremental

Drug Development Timeline



*Not drawn to scale

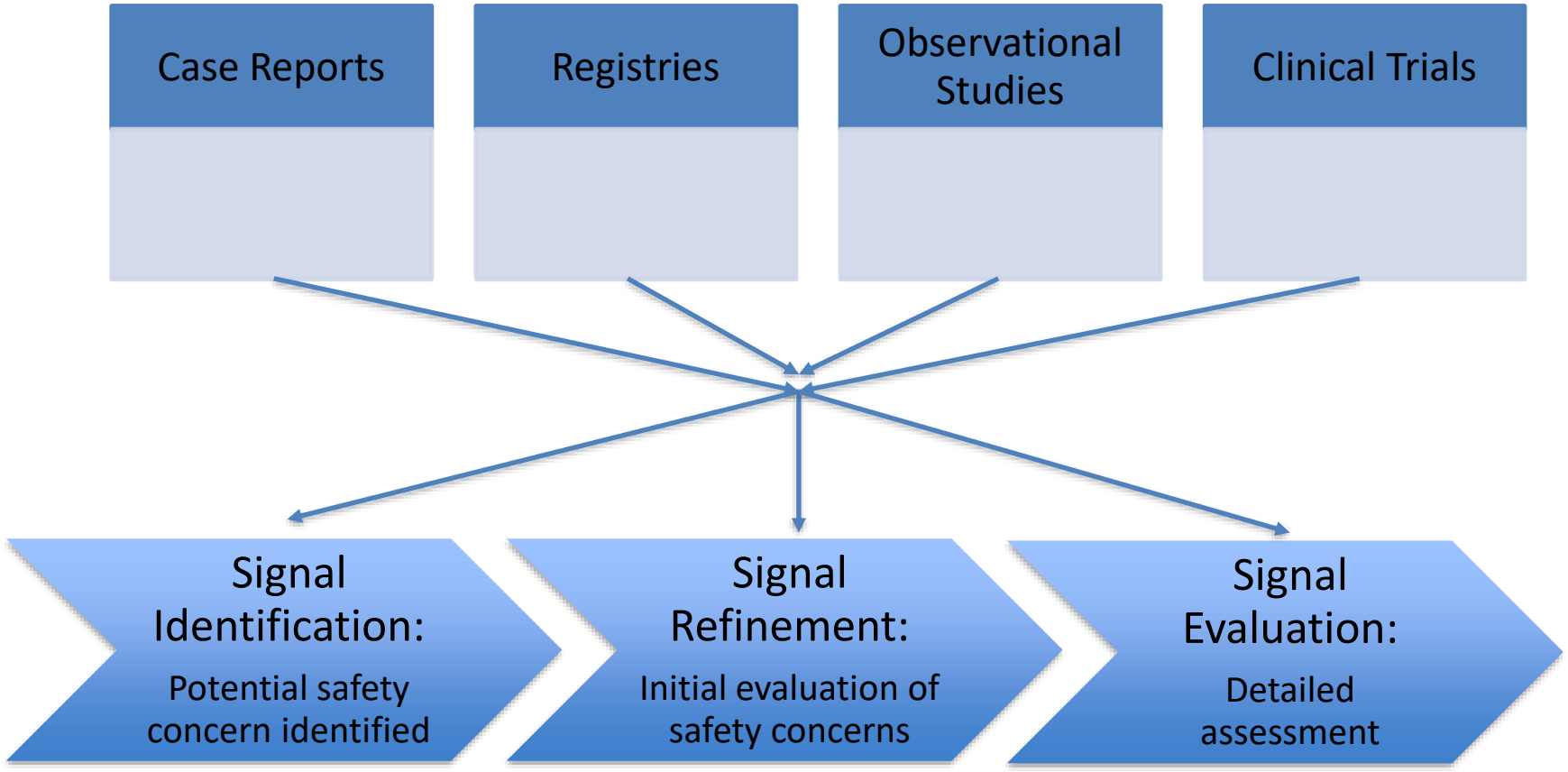
Main Sources of Postmarket Drug Safety Data

Case Reports	Registries	Observational Studies	Clinical Trials
• Individual case reports • From the point of care • Mostly via industry • Sometimes from literature	• Defined populations • Disease-based or drug based • Various sponsors	• Often based on large databases • Led by industry, academia, or FDA	• Sometimes specifically for safety • Mostly industry-sponsored

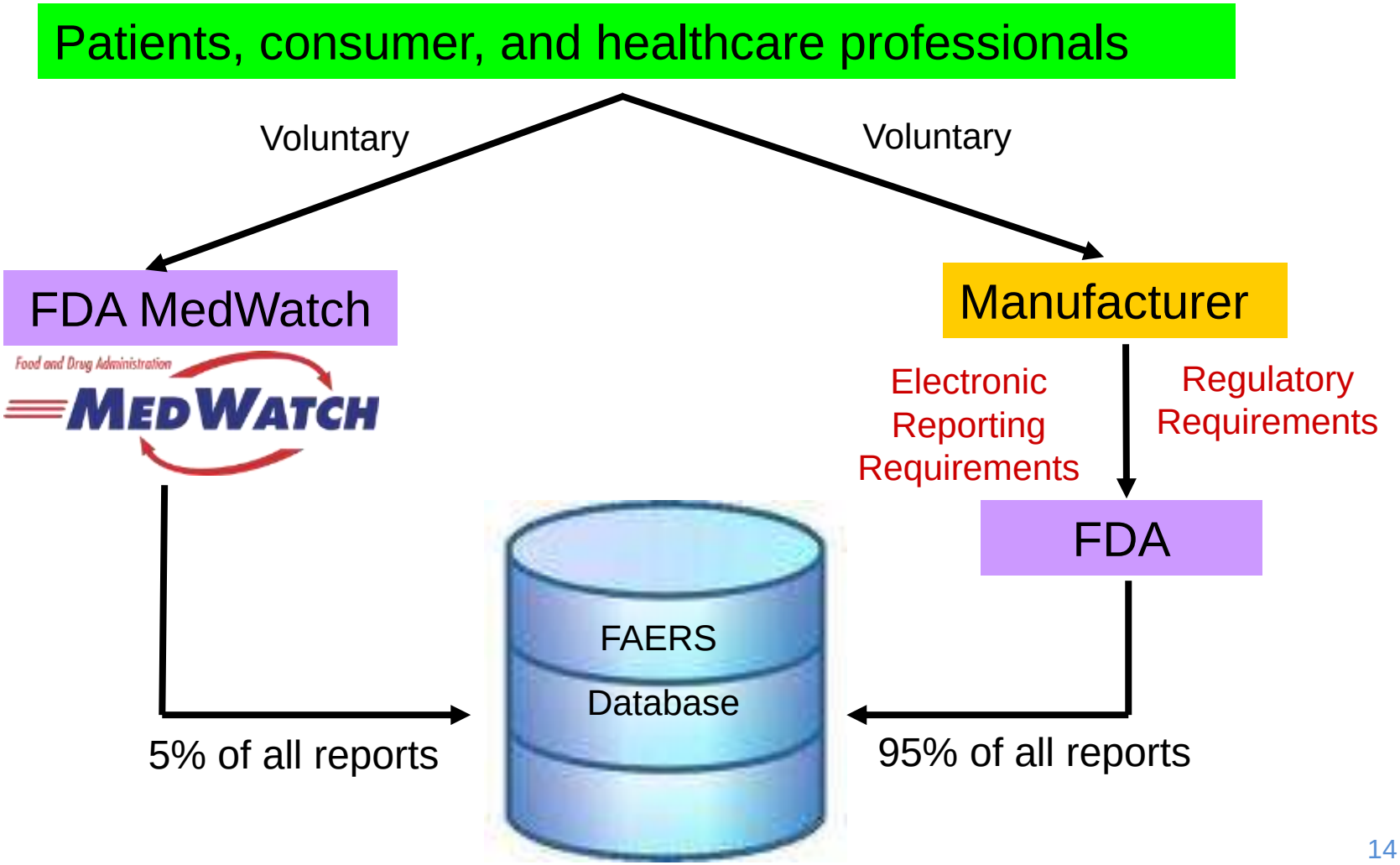
Information from these data sources are used together to provide as complete as possible an understanding of the risk of a drug.

Post-Market Safety Assessment

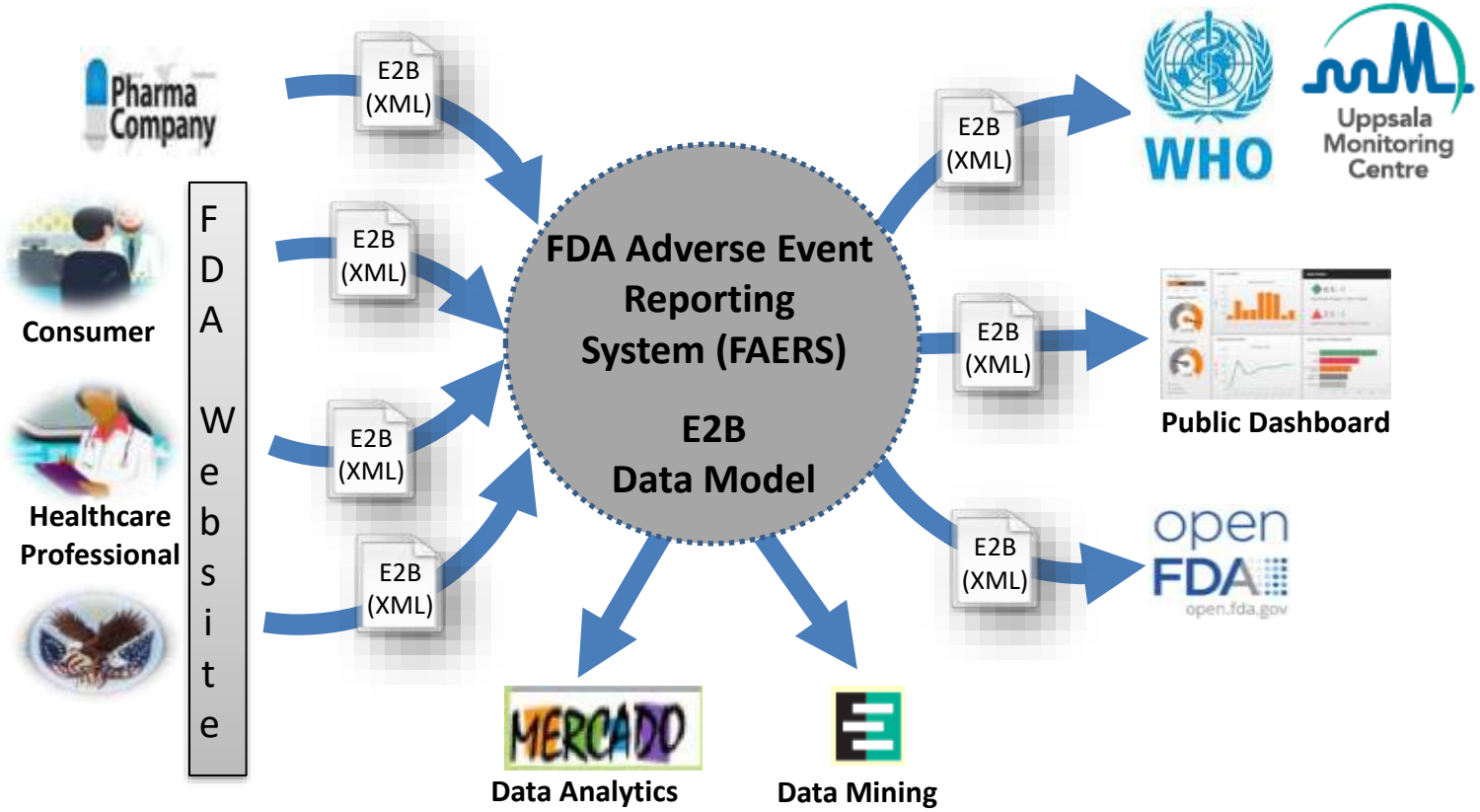
What Gives Rise to Signals at FDA



How Postmarketing Reports Get to FDA

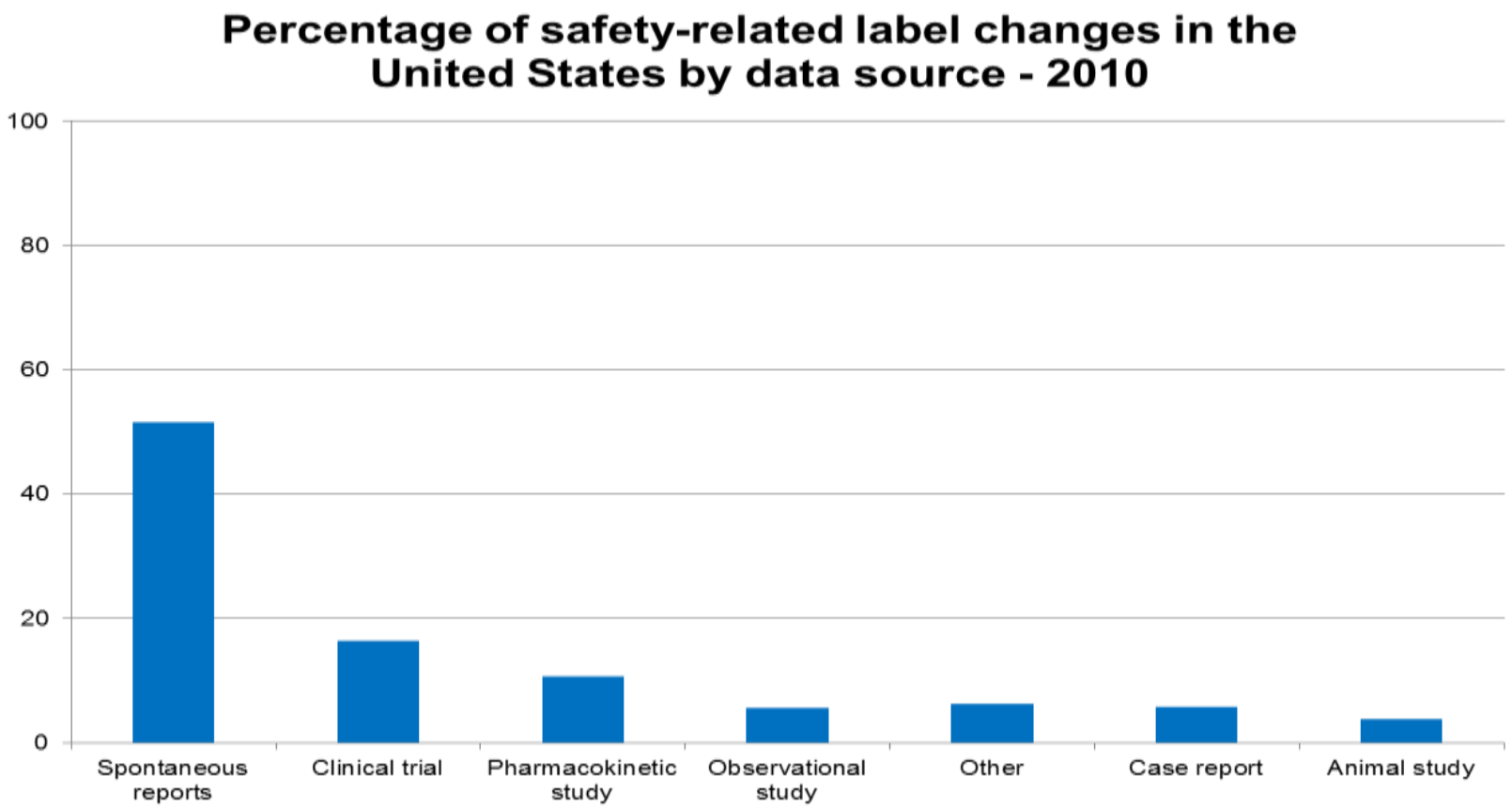


Uses of ICH E2B at US FDA



FDA Adverse Event Reporting System (FAERS)

Safety Labeling Changes



Source: Lester et al. Pharmacoepidemiol Drug Safety 2013 Mar;22(3):302-5

Can Natural Language Processing Aide the Evaluation of Clinical Texts?

- Natural Language Processing (NLP) combines:
  - Computer science
  - Artificial intelligence
  - Computational linguistics
- Can NLP Improve the efficiency and scientific validity of clinical text analysis?
  - e.g. application to narratives of individual case safety reports for pharmacovigilance
  - Many other potential uses in drug safety across the drug lifecycle (eg, reading articles from the medical literature)

Selected Contexts in which Clinical Texts Arise

- IND safety reports
- NDA/BLA submissions
  - Trials
    - Patient identification/enrollment
    - Data collection (e.g. auto populate CRF's)
- Labels
  - Is an adverse event "labeled"?
- Post-market Individual Case Safety Reports of Adverse Events
  - Key information often in clinical narratives
- Pharmacoepidemiological studies
  - Sentinel System
- Social Media/Internet query logs

Can Social Media Generate Signals?

Drug Saf (2014) 37:343–350
DOI 10.1007/s40264-014-0155-x

ORIGINAL RESEARCH ARTICLE

Digital Drug Safety Surveillance: Monitoring Pharmaceutical Products in Twitter

Clark C. Freifeld · John S. Brownstein · Christopher M. Menone · Wenjie Bao · Ross Filice · Taha Kass-Hout · Nabarun Dasgupta

- English-language Twitter posts mentioning 23 medical products
- Identified posts resembling adverse events (proto-Aes)
- Vernacular internet terms translated to MedDRA
- Terms aggregated by MedDRA SOC
- 4,401 proto-Aes idnetified
- High correlation with FAERS at SCO level

Author's conclusion:

"Patients reporting AEs on Twitter showed a range of sophistication when describing their experience. Despite the public availability of these data, their appropriate role in pharmacovigilance has not been established. Additional work is needed to improve data acquisition and automation."

Source: Freifeld et al. Drug Saf 2014; 37:343-350

Real-world Evidence

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

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Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D.,
Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D.,
Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

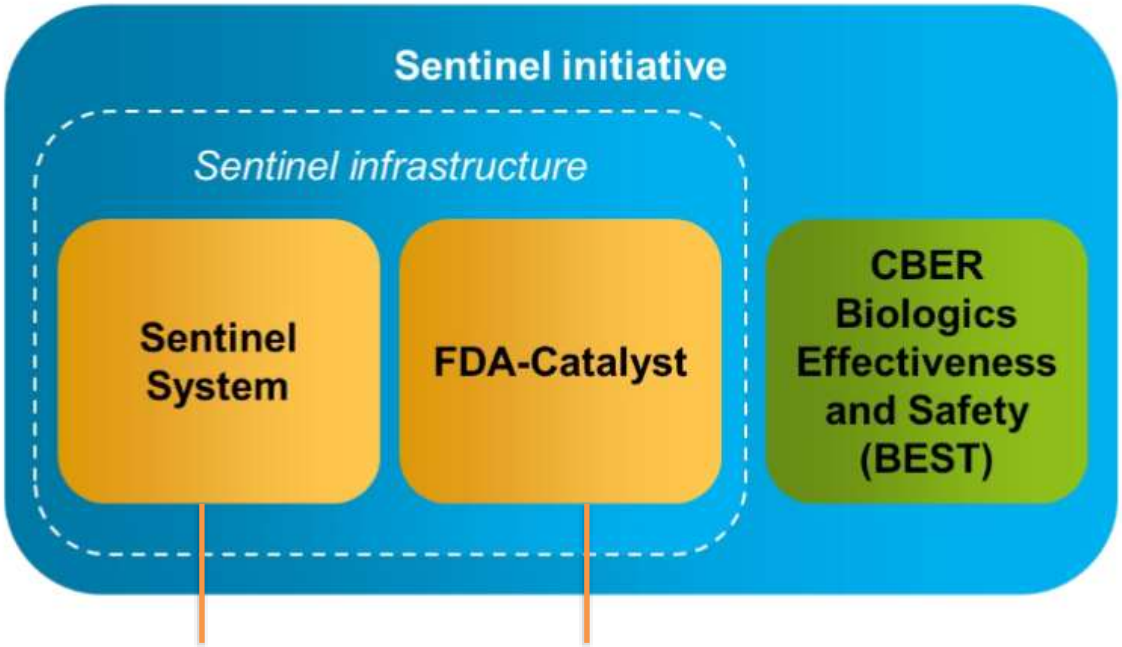
CDER Definitions

- **Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.**
- **Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.**

RWD include data derived from electronic health records (EHRs), claims and billing

RWE can be generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Components of Sentinel Initiative



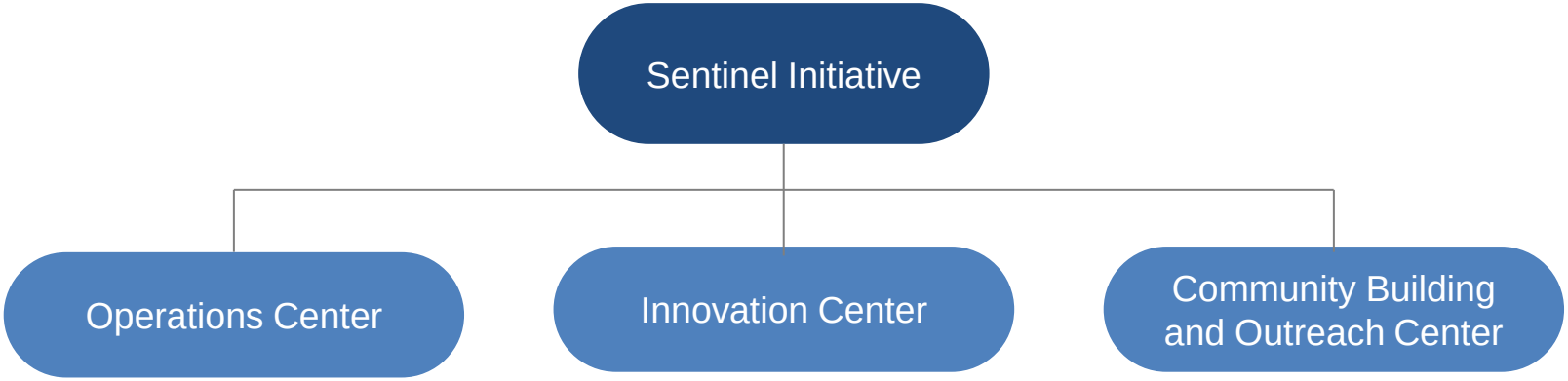
Queries using predefined analytic tools and distributed data network

Routine queries + interventions or interactions with health plan members

Key Messages from the Sentinel Strategic Plan – 2019

- Maintain and enhance the foundation of the Sentinel System, preserving FDA's long term investment in Sentinel's analysis tools and data infrastructure
- Diversify data sources, especially EHRs and claims linked to EHR
- Selectively incorporate advanced analytics
- Broaden touch points for participating in Sentinel's development
- Establish a Sentinel scientific community and disseminate knowledge to improve public health

New Sentinel System Structure



Enhance the Infrastructure

- Enhance core data sources, evolve the CDM
- Develop novel distributed analysis tools
- Further enhance capabilities in signal detection and other areas
- Lead RWE demonstration projects through FDA Catalyst

Advance the Science

- Improve capabilities by leveraging advances in data science and advanced analytics
- Explore new ways to access and structure EHR data
- Expand access to novel data sources such as patient data, wearable devices, registries
- Improve CDM interoperability

Engage the Community

- Catalyze breakthrough ideas around enduring problems through scientific competitions
- Modernize or develop new public portals to enhance search, information management, community engagement
- Accelerate use of Sentinel System for uses beyond product safety

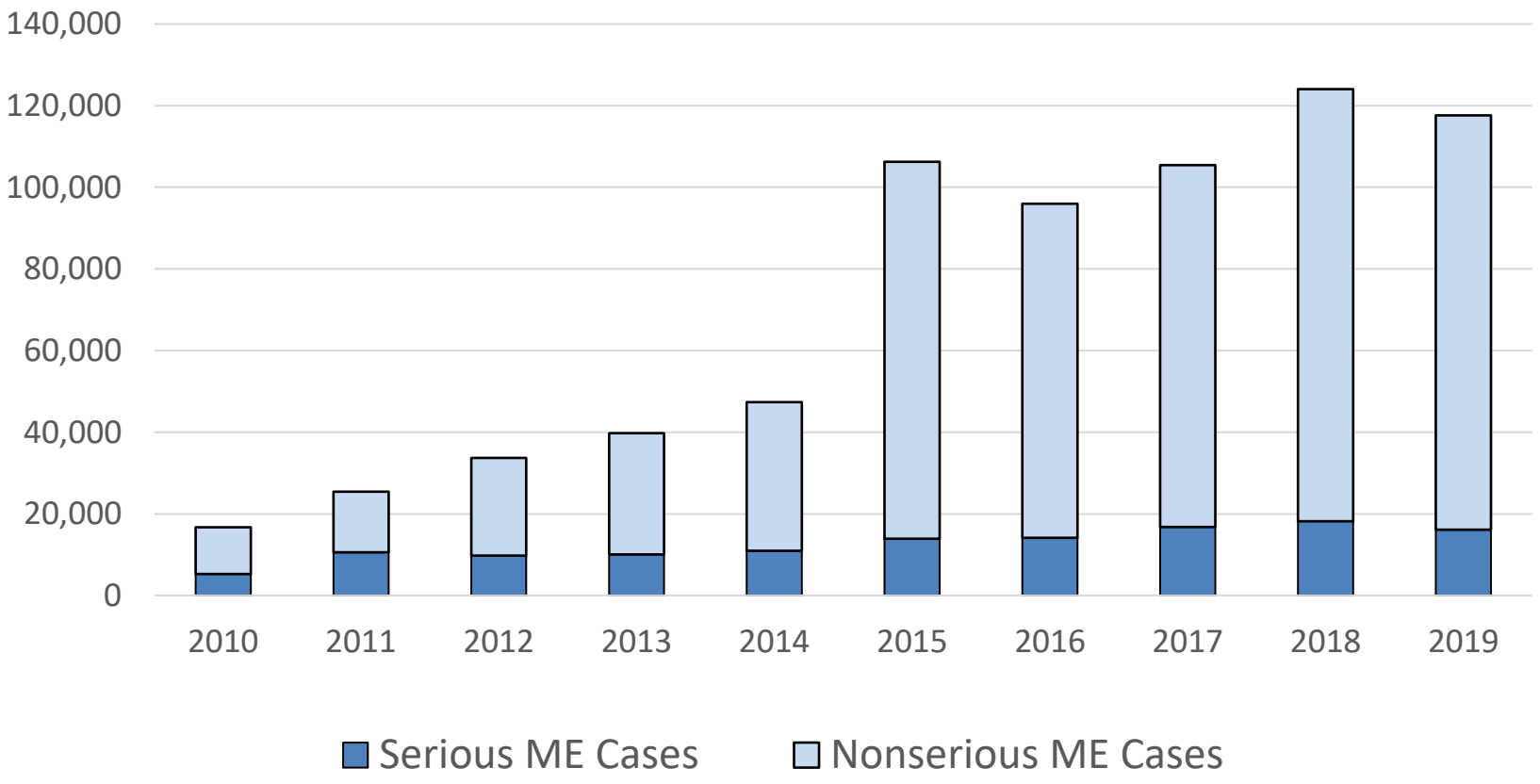
Medication Errors are a Global Public Health Burden

$21 BILLION	Estimated annual cost of U.S. outpatient and inpatient preventable medication errors
52%	Among adult outpatients…**52% (95% CI: 42–62%)** of adverse drug reactions were **preventable**
45%	Among inpatients…**45% (95% CI: 33–58%)** of adverse drug reactions were **preventable [errors]**

Network for Excellence in Health Innovation. Dec 2011. Available from: http://www.nehi.net/bendthecurve/sup/documents/Medication_Errors_%20Brief.pdf

Hakkarainen KM, et. al., Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. PLoS One. 2012.

Number of U.S. Medication Error Cases Submitted to FAERS*



*FAERS=FDA Adverse Event Reporting System; ME=Medication Error
Case counts based on the MedDRA SMQ *Medication errors (narrow)*, V 22.1

WHAT DO WE DO?

DMEPA Review Activities

Reviews take into account current federal regulations, applicable Guidance for Industry, USP Standards, and relevant postmarket experience.

- **PROPRIETARY NAMES**
  Primary/signatory authority on review of proprietary names.
- **NONPROPRIETARY NAME SUFFIX**
- **PRODUCT LABELING**
- **PRODUCT PACKAGING**
- **HUMAN FACTORS/ PRODUCT DESIGN**
  Primary/signatory authority on human factors protocols.
- **POSTMARKET PHARMACOVIGILANCE**

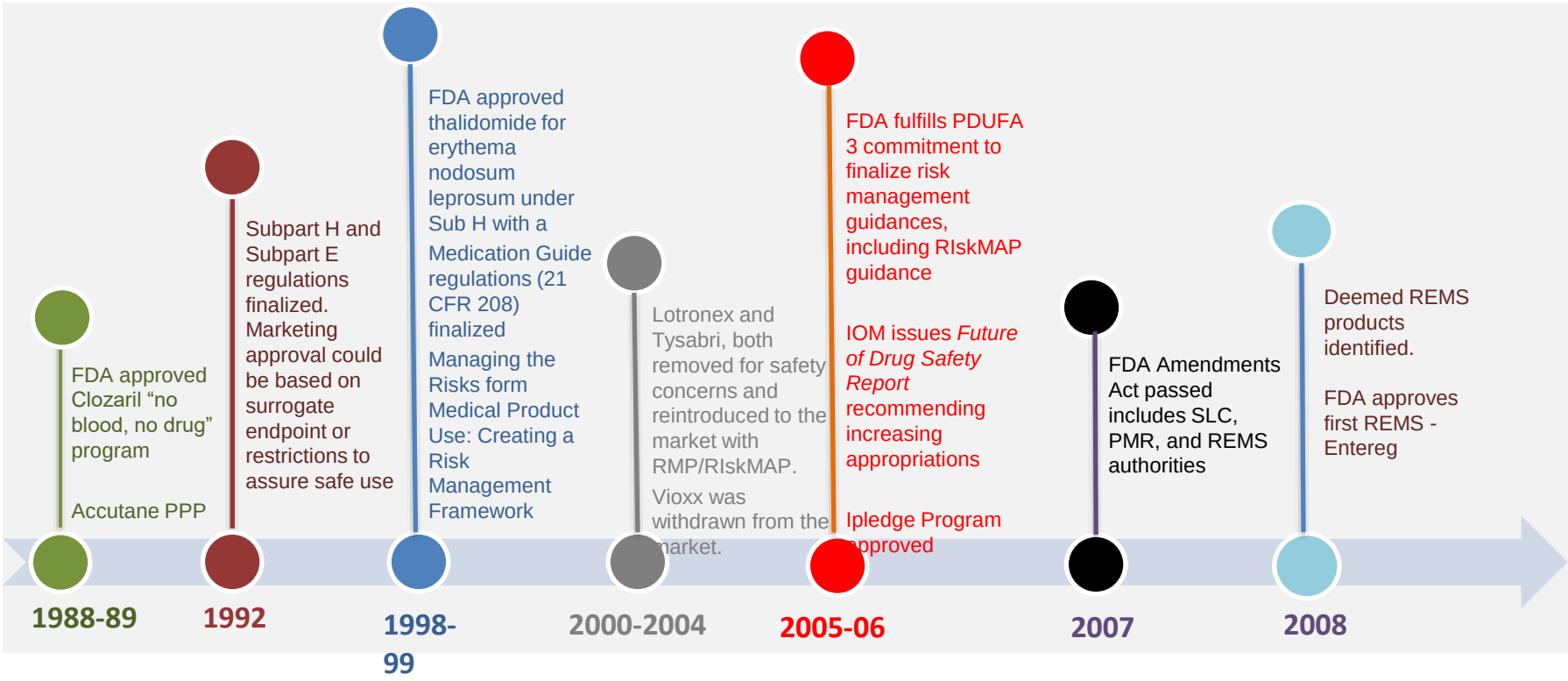
FDA's Role in Risk Management Programs

FDA has experience with risk management programs for over 30 years

A variety of terms have been used:

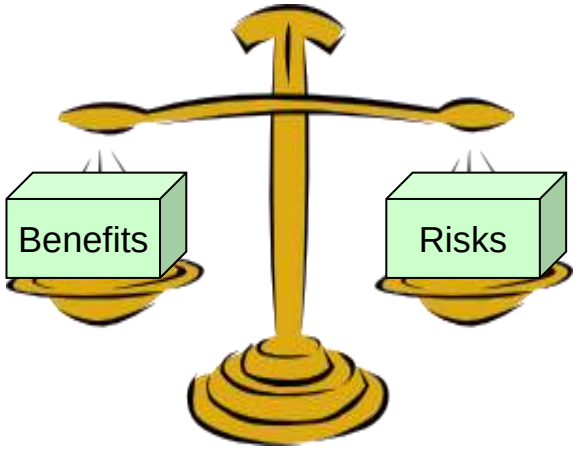
- Risk Management Programs
- Risk Minimization Action Plan (RiskMAP)
- Risk Evaluation and Mitigation Strategies (REMS)

FDA Risk Management – Historical Timeline



What is a REMS?

- **R**isk **E**valuation and **M**itigation **S**trategy
- A risk management plan that uses risk minimization strategies beyond professional labeling.
- Designed to achieve specific goals to mitigate risks associated with use of a drug.
- Required to ensure that the benefits of the drug outweigh the risks.



Components of a REMS

- A REMS can include
  - Medication Guide or PPI
  - Communication Plan for Healthcare Providers (HCPs)*
  - Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
  - Elements to Assure Safe Use (ETASU)
    - May include restricted distribution
  - Implementation System

- Must include a timetable for submission of assessments of the REMS*

**Note: This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS*

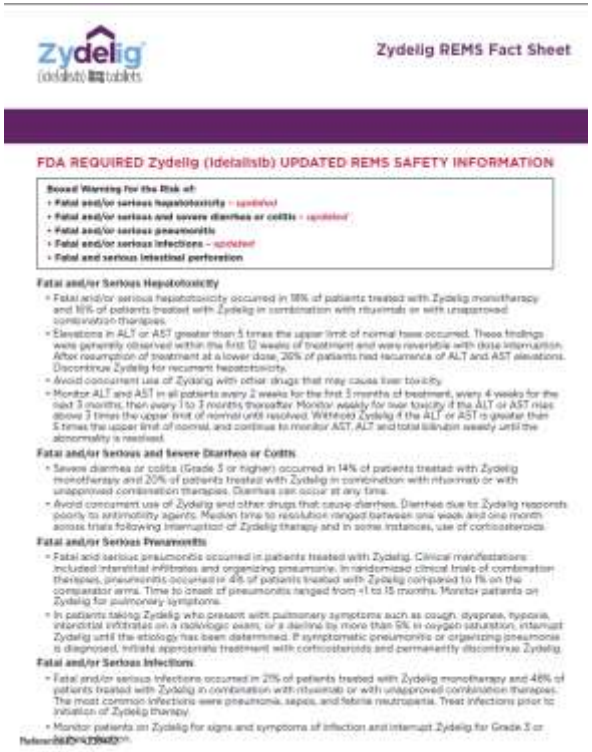
Medication Guides

- Patient-friendly paper handouts that are required* to be handed out with many prescription **medicines**.
- Medication Guides also approved as part of labeling
- Initial policy was to approve all new Medication Guides or those with significant new safety information as an element of a REMS
- Guidance for Industry reversed that policy
  - Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) https://www.fda.gov/media/79776/download

**The requirements of Medication Guides are contained in the Code of Federal Regulations, 21 CFR 208.*

Communication Plans

- FDA approved materials used to aid sponsor's implementation of a REMS and/or inform healthcare providers about serious risks
  - Cannot be targeted directly to patients
- Communication plan may include:
  - REMS drug fact sheet
  - Letters to professional societies or healthcare providers
  - Patient Safety Information that prescribers can use to counsel patients or to provide to patients



Zydelig (idelalisib) tablets

Zydelig REMS Fact Sheet

FDA REQUIRED Zydelig (idelalisib) UPDATED REMS SAFETY INFORMATION

Boxed Warning for the Risk of:
- Fatal and/or serious hepatotoxicity – updated
- Fatal and/or serious and severe diarrhea or colitis – updated
- Fatal and/or serious pneumonitis
- Fatal and/or serious infections – updated
- Fatal and serious intestinal perforation

Fatal and/or Serious Hepatotoxicity

- Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 16% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies.
- Elevations in ALT or AST greater than 5 times the upper limit of normal have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Discontinue Zydelig for recurrent hepatotoxicity.
- Avoid concurrent use of Zydelig with other drugs that may cause liver toxicity.
- Monitor ALT and AST in all patients every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 3 times the upper limit of normal until resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

Fatal and/or Serious and Severe Diarrhea or Colitis

- Severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of patients treated with Zydelig monotherapy and 20% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. Diarrhea can occur at any time.
- Avoid concurrent use of Zydelig and other drugs that cause diarrhea. Diarrhea due to Zydelig responds poorly to antimotility agents. Median time to resolution ranged between one week and one month across trials following interruption of Zydelig therapy and in some instances, use of corticosteroids.

Fatal and/or Serious Pneumonitis

- Fatal and serious pneumonitis occurred in patients treated with Zydelig. Clinical manifestations included interstitial infiltrates and organizing pneumonia. In randomized clinical trials of combination therapies, pneumonitis occurred in 4% of patients treated with Zydelig compared to 1% on the comparator arms. Time to onset of pneumonitis ranged from <1 to 15 months. Monitor patients on Zydelig for pulmonary symptoms.
- In patients taking Zydelig who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, interrupt Zydelig until the etiology has been determined. If symptomatic pneumonitis or organizing pneumonia is diagnosed, initiate appropriate treatment with corticosteroids and permanently discontinue Zydelig.

Fatal and/or Serious Infections

- Fatal and/or serious infections occurred in 21% of patients treated with Zydelig monotherapy and 48% of patients treated with Zydelig in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis, and febrile neutropenia. Treat infections prior to initiation of Zydelig therapy.
- Monitor patients on Zydelig for signs and symptoms of infection and interrupt Zydelig for Grade 3 or

Drug Packaging and Disposal

- **Section 3032 Of the SUPPORT Act provider FDA new REMS Authority:** FDA may require unit dose packaging "that provides a set duration" and/or "safe disposal packaging," to be dispensed to certain patients if FDA determines that doing so "may mitigate [a] serious risk" of an adverse drug experience occurring from abuse or overdose
- **Potential Burdens:** FDA must consider potential burdens on patient access and the healthcare system

Elements to Assure Safe Use

- ETASU are medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

- Depending on the risk, a REMS may require one or more of the following:
  - Prescribers have specific training/experience or special certifications (ETASU A)
  - Pharmacists or other dispensers be specially certified (ETASU B)
  - Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals) (ETASU C)
  - Drug be dispensed with evidence of safe-use conditions such as laboratory test results (ETASU D)
  - Each patient using the drug be subject to monitoring (ETASU E)
  - Each patient using the drug be enrolled in a registry (ETASU F)

Implementation System

- REMS may include an implementation system related to these ETASU:
  - (B) certification of pharmacies and hospitals
  - (C) healthcare settings
  - (D) safe use conditions
- May require applicant to take reasonable steps to—
  - monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
  - work to improve implementation of such elements by such persons

REMS Assessments

- Timetable for submission of assessments
  - NDA and BLA assessment submissions
    - 18 months, 3 years, and in the 7th year after the strategy is initially approved
    - At a frequency specified in the strategy; can be increased or reduced in frequency and eliminated under certain circumstances
  - Typical timetables
    - Most MG and CP REMS - 18 months, 3 years, 7 years
    - REMS with ETASU - 6 and 12 months following approval, and annually thereafter

Thank you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