Applying Innovative Approaches to Monitoring Neonatal Therapeutics

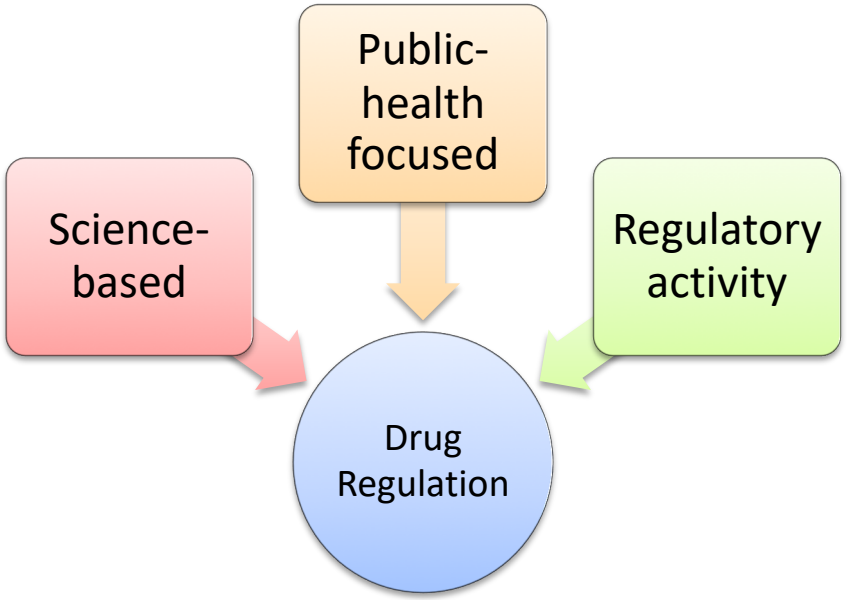
Gerald J. Dal Pan, MD, MHS
Director
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

International Neonatal Consortium
North Bethesda, Maryland
12 April 2018

No conflicts of interest to disclose

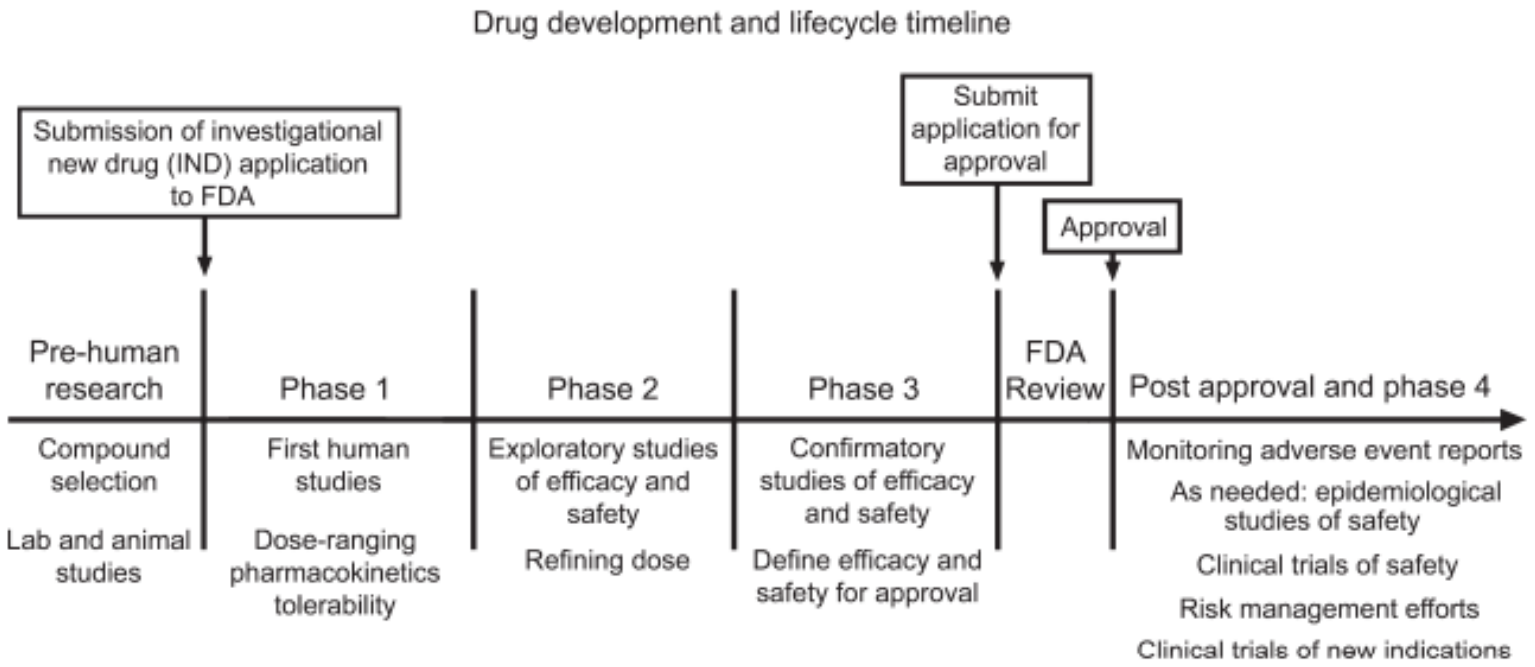
Role of the Drug Regulator

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



Drug Lifecycle

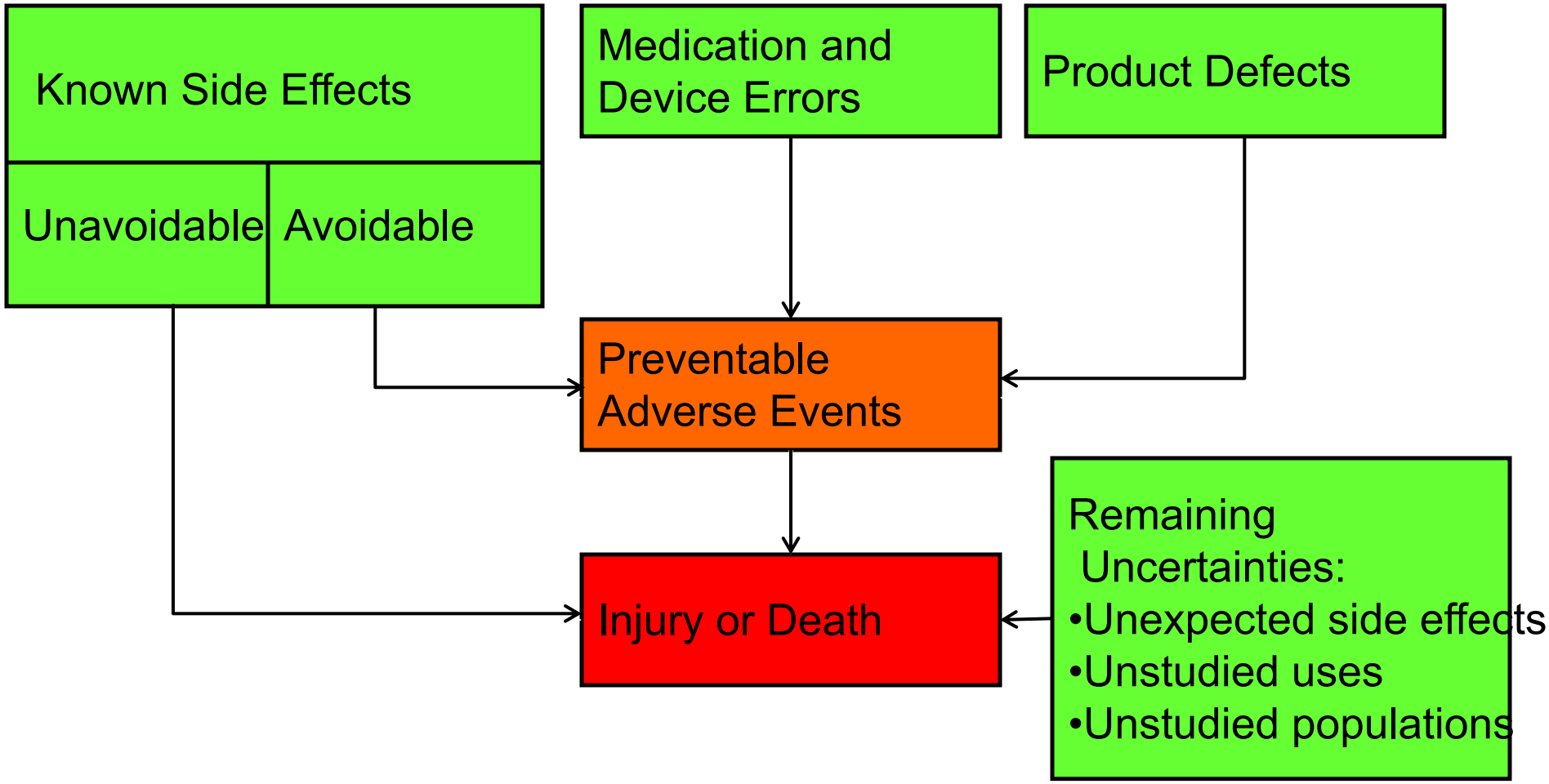
Figure **Drug development and lifecycle timeline**



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.

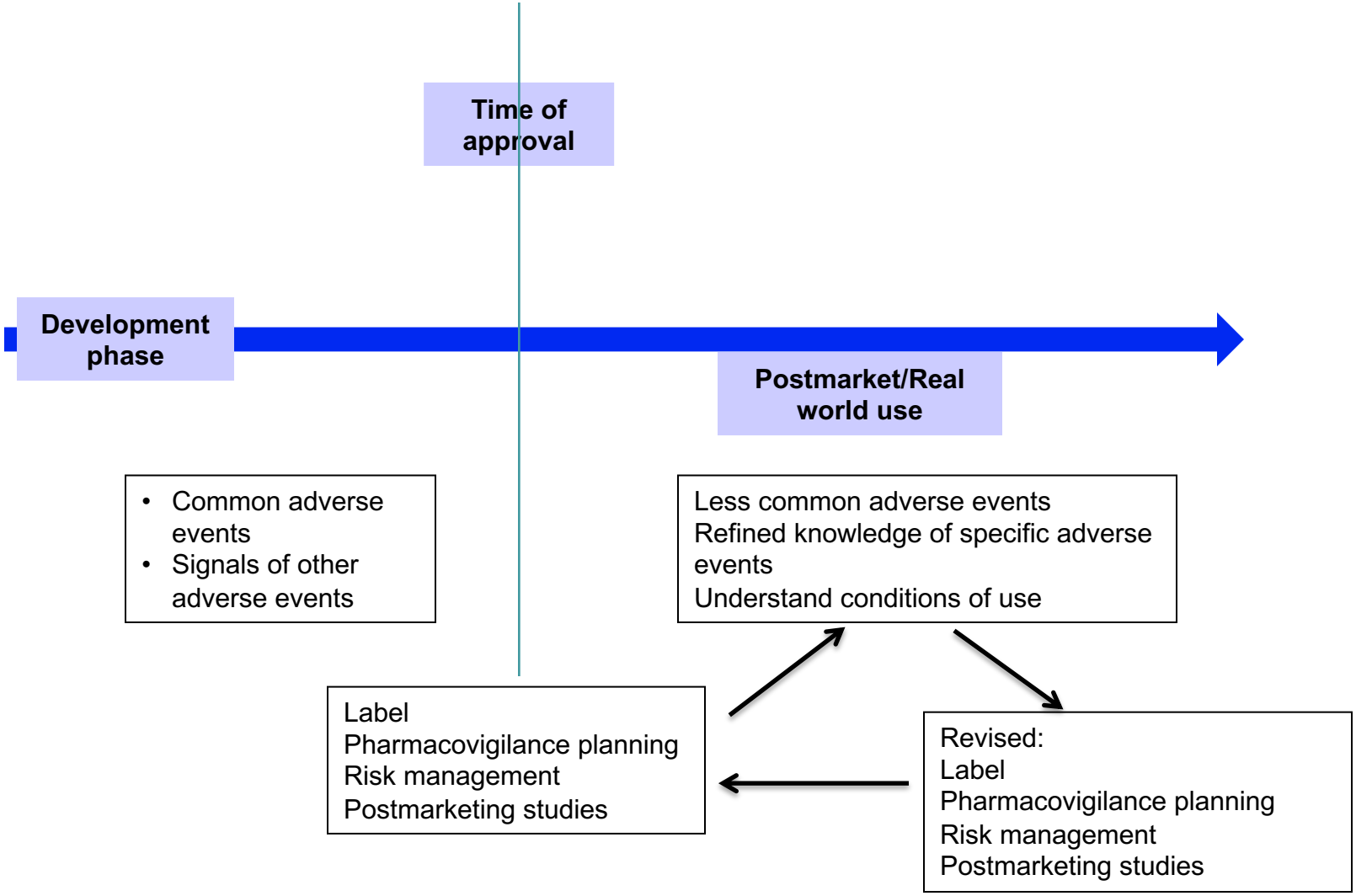
Source: Dal Pan GJ. The US Food and Drug Administration, neurologists, and drug development and regulation. Neurology Clinical Practice 2015;5:338-343.

Sources of Risk From Medical Products



What We Want to Learn

Lifecycle of drug safety knowledge



This process is iterative and incremental

Drug Labels Contain Important Safety-related Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- **[text]**
- **[text]**

----------**RECENT MAJOR CHANGES**----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------**INDICATIONS AND USAGE**----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------**DOSAGE AND ADMINISTRATION**----------
- [text]
- [text]

----------**DOSAGE FORMS AND STRENGTHS**----------
- [text]

----------**CONTRAINDICATIONS**----------
- [text]
- [text]

----------**WARNINGS AND PRECAUTIONS**----------
- [text]
- [text]

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------**DRUG INTERACTIONS**----------
- [text]
- [text]

----------**USE IN SPECIFIC POPULATIONS**----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

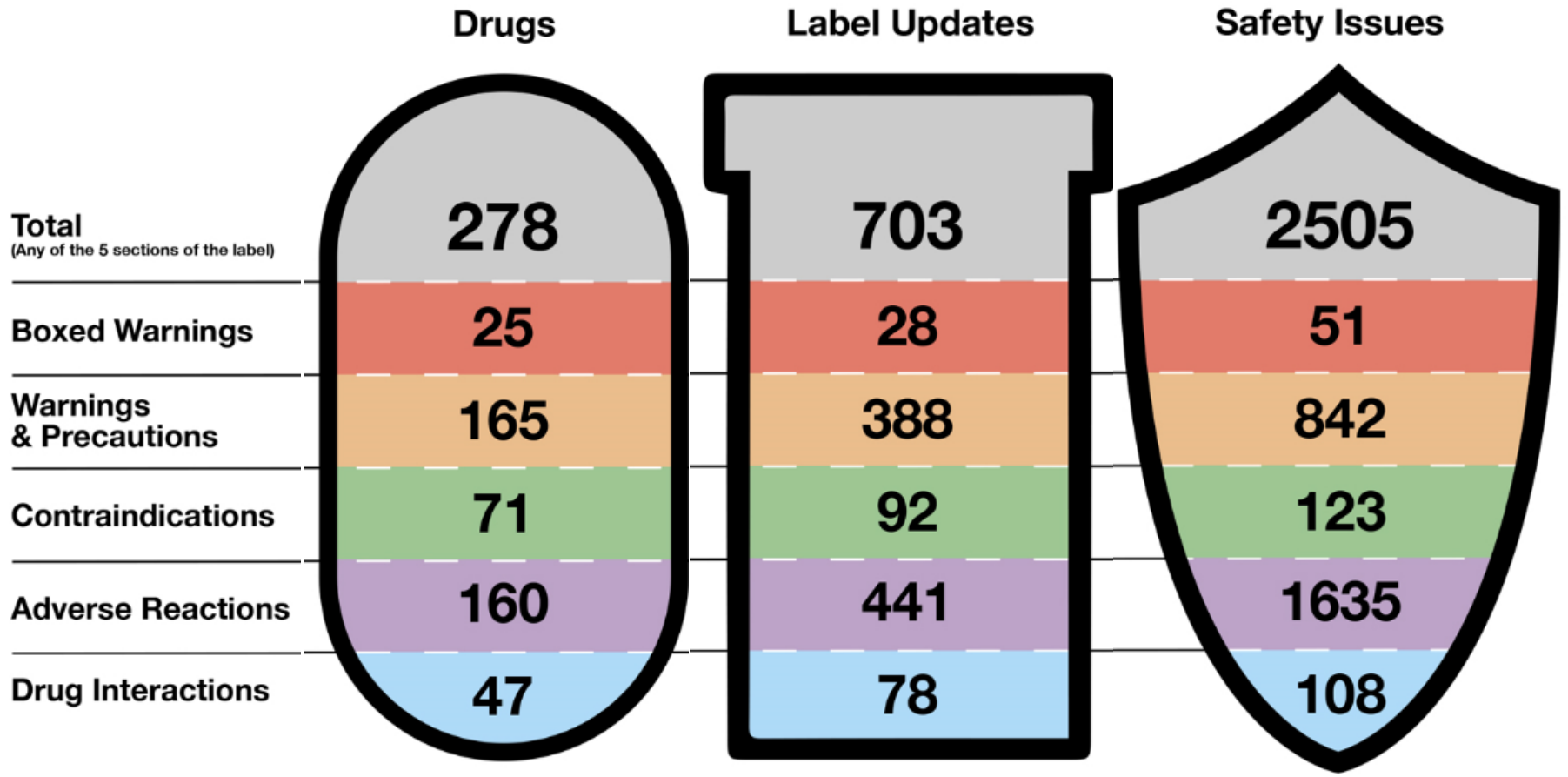
Revised: [m/year]

Safety-related Label Changes

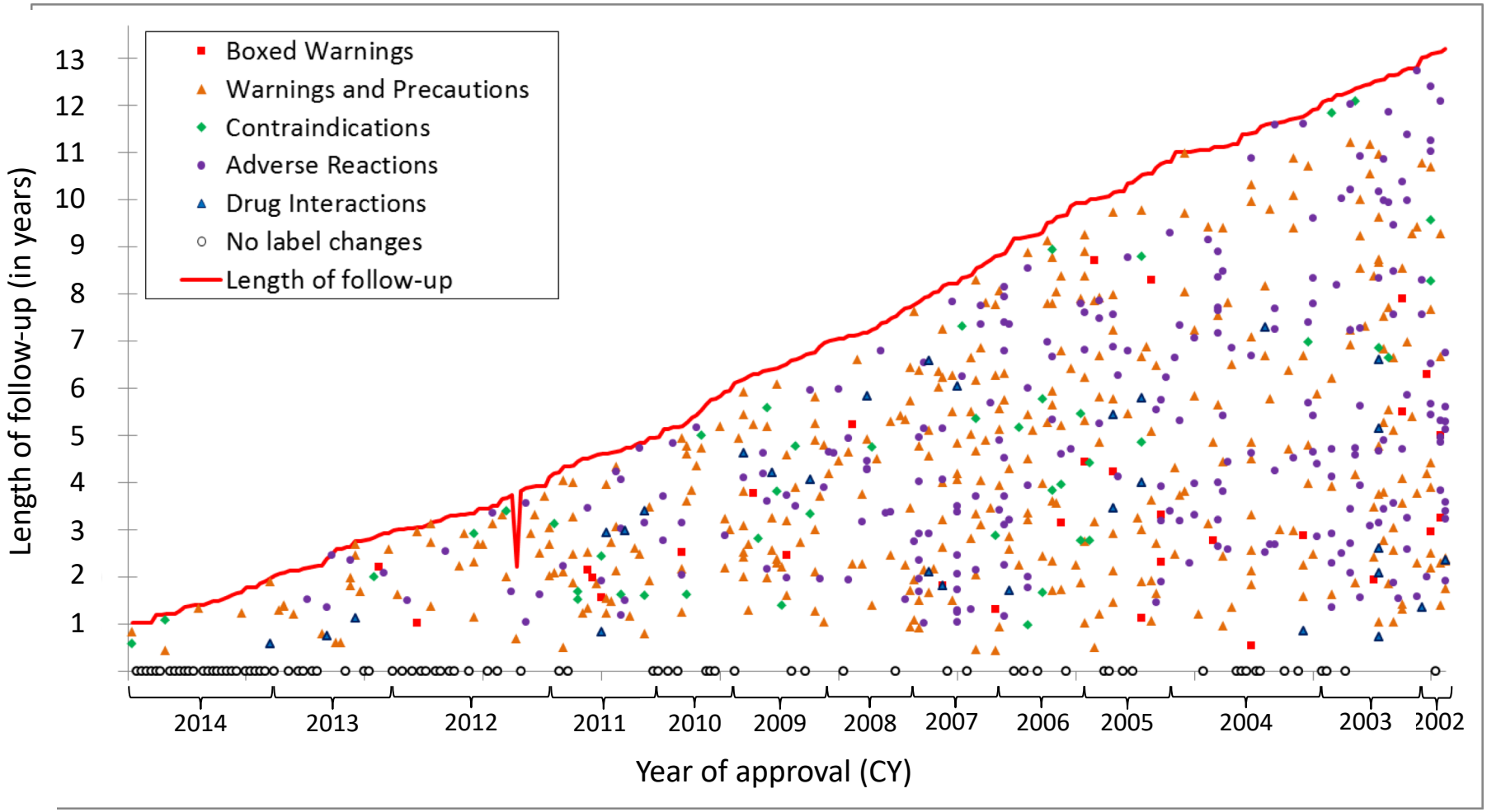
- 278 NMEs approved between October 1, 2002 and December 31, 2014.
- 1 safety withdrawal
- 195 (70.1%) with ≥ 1 safety outcome
- 83 (29.9%) no safety related label change or withdrawal

Results

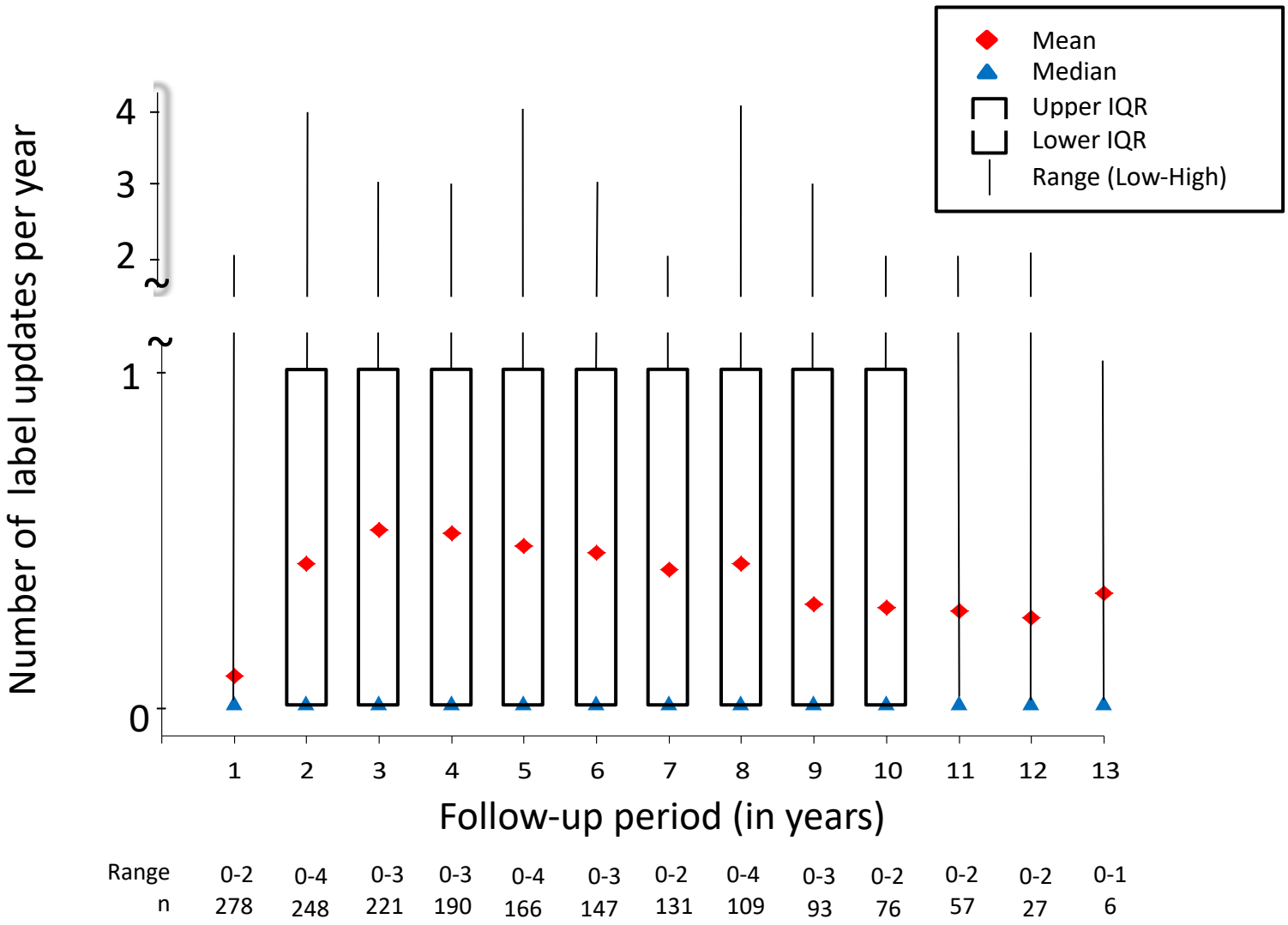
Total: 278 Drugs



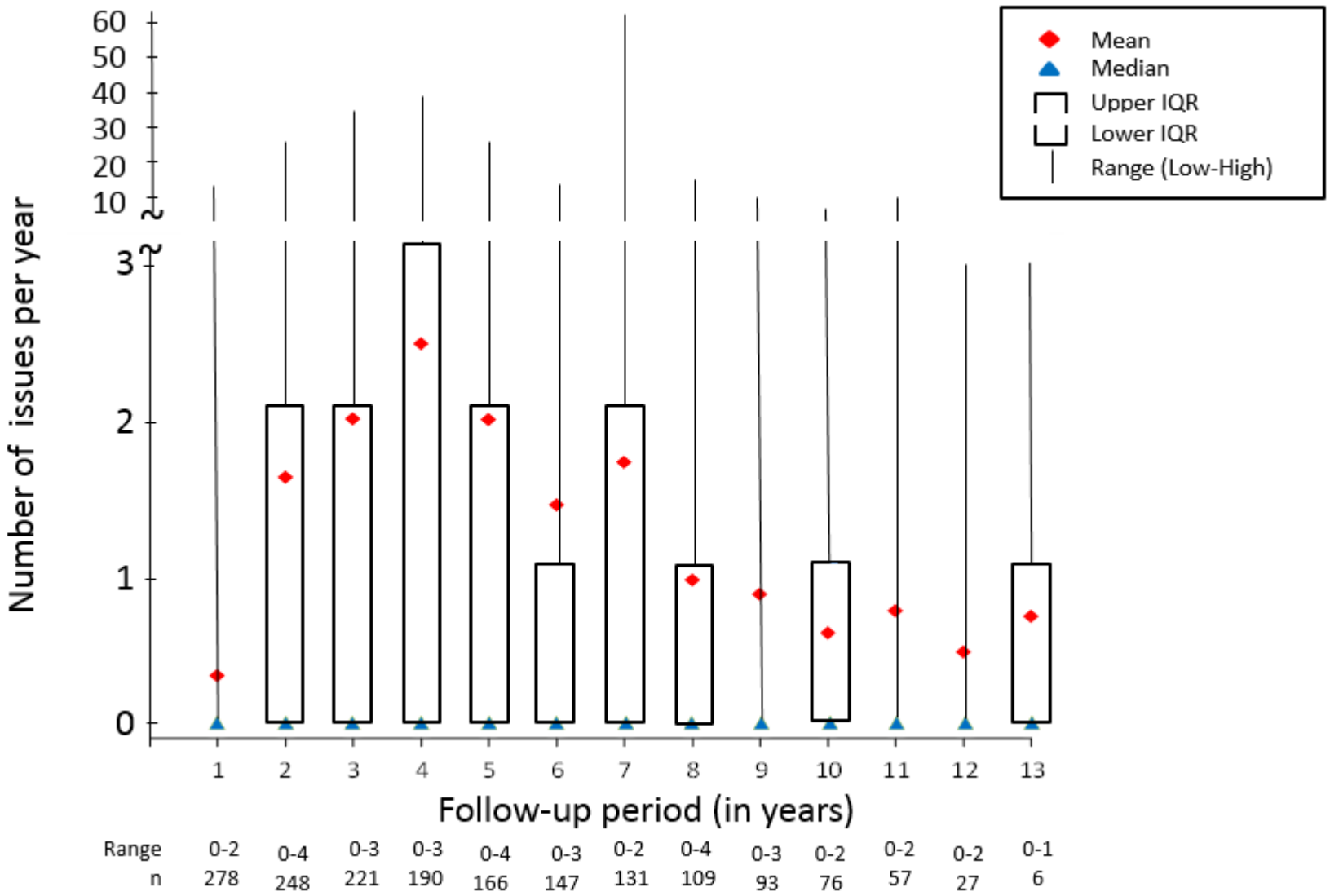
Hierarchical presentation of time to drug label updates for NMEs by section of the label updated as of December 31, 2015



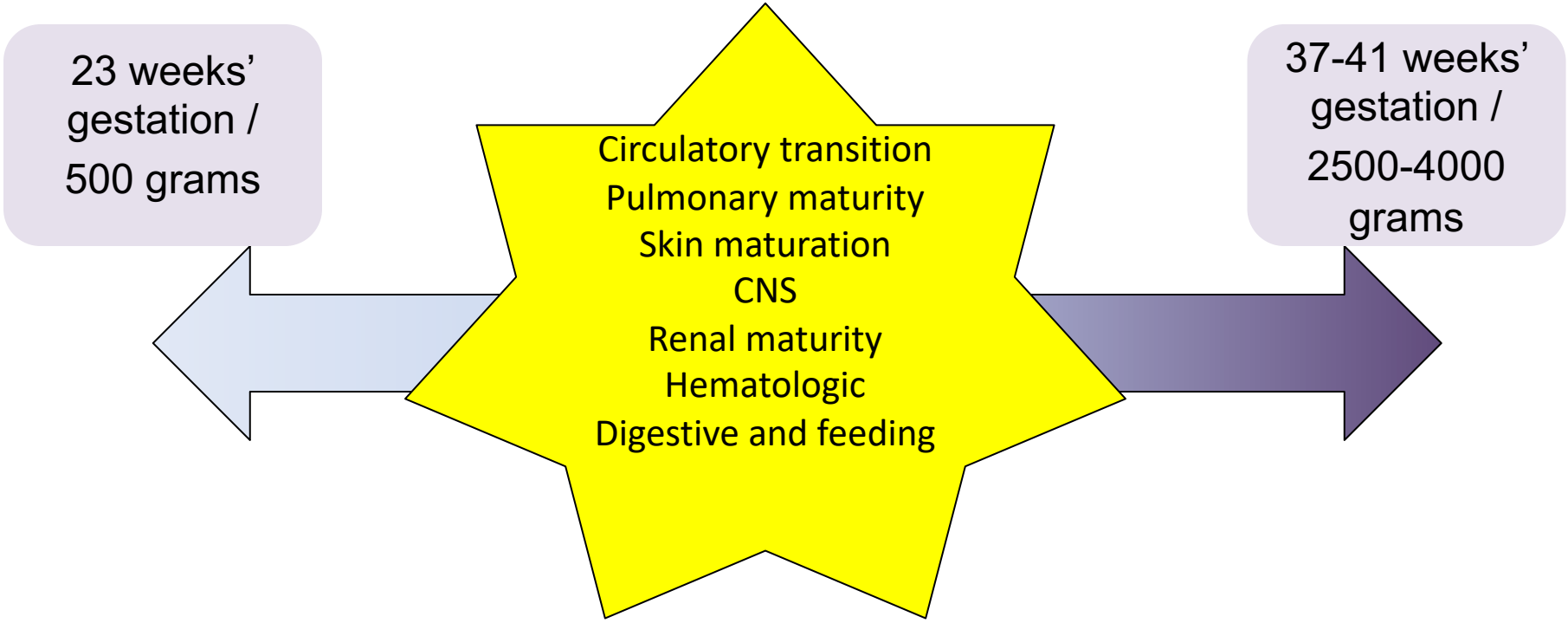
Average number of label updates per year of follow-up



Average number of issues per year of follow-up



Special Considerations in Neonates



Drug Utilization

Patterns of Drug Utilization in a Neonatal Intensive Care Unit

Indulekha Warrier, MD, Wei Du, PhD, Girija Natarajan, MD,
Vali Salari, PhD, and Jacob Aranda, MD, PhD

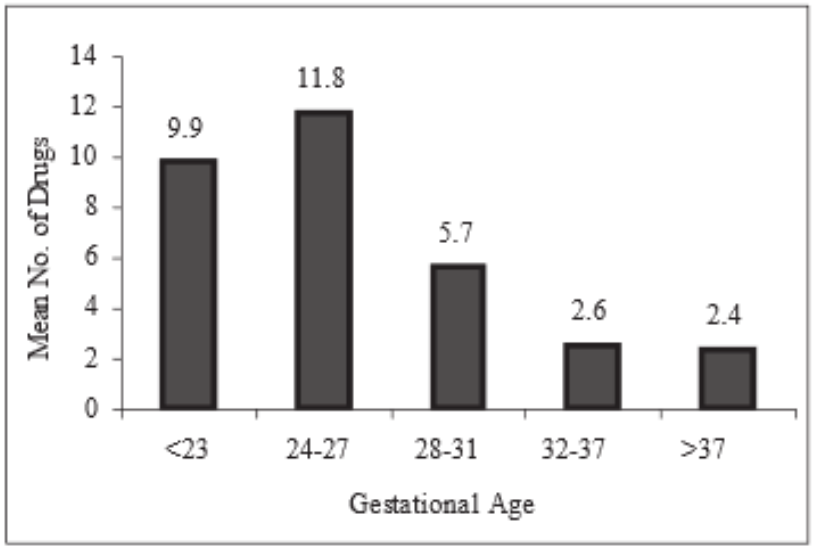


Figure 1. Mean drug use by gestational age.

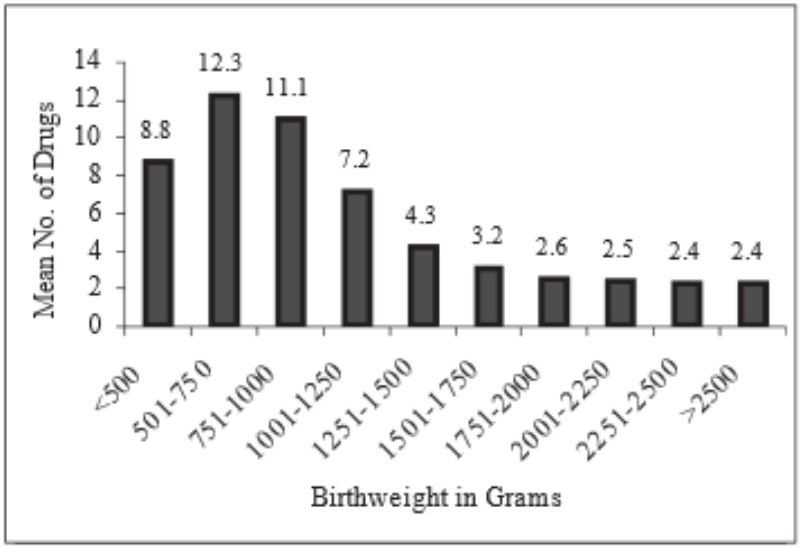


Figure 2. Mean drug use by birthweight.

Source: Warrier I, Du W, Natarajan G, et al. 2006. Patterns of drug utilization in a neonatal intensive care unit. J. Clin. Pharmacol. 46:449-455.

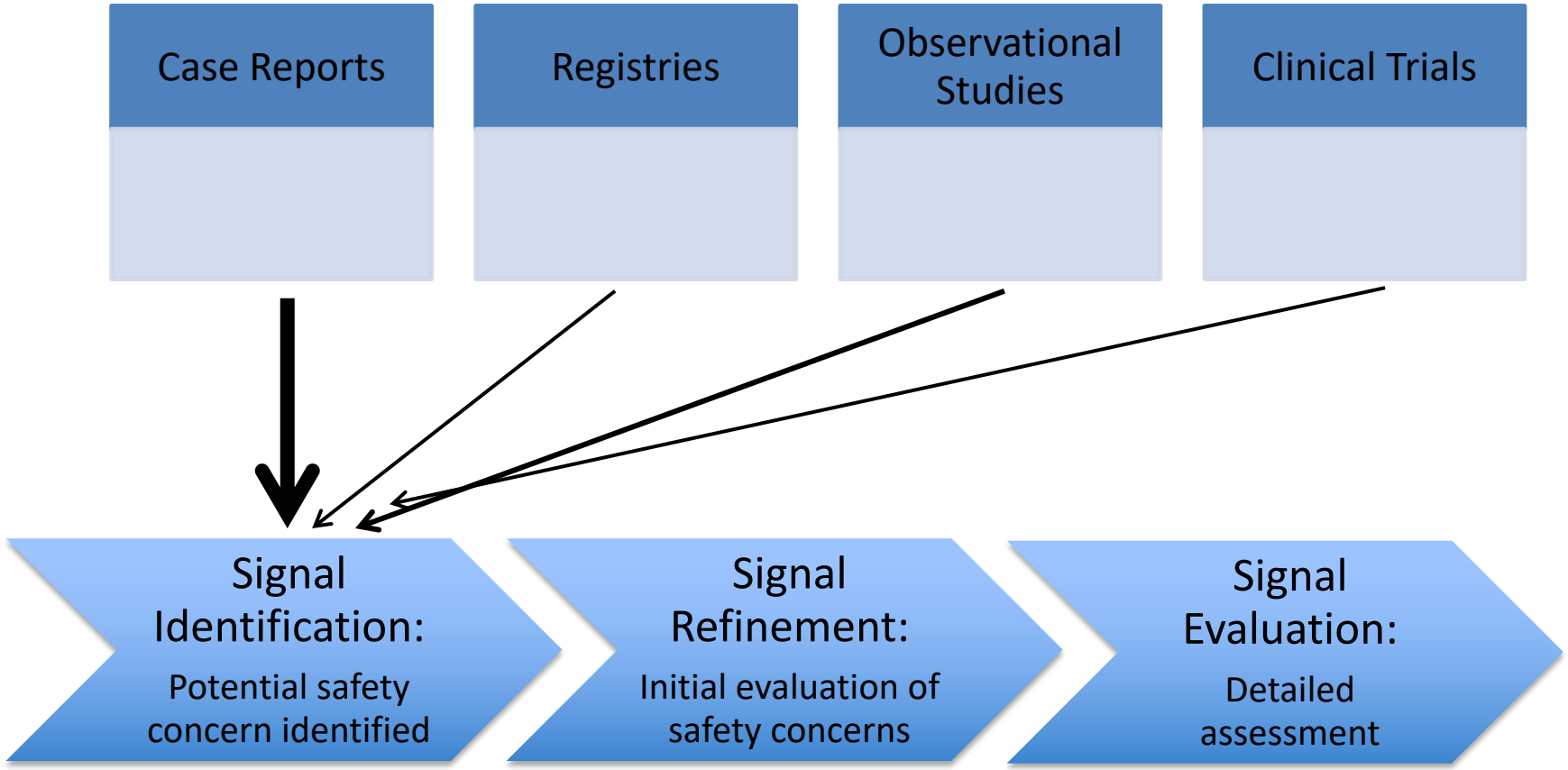
Main Sources of Drug Safety Data

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

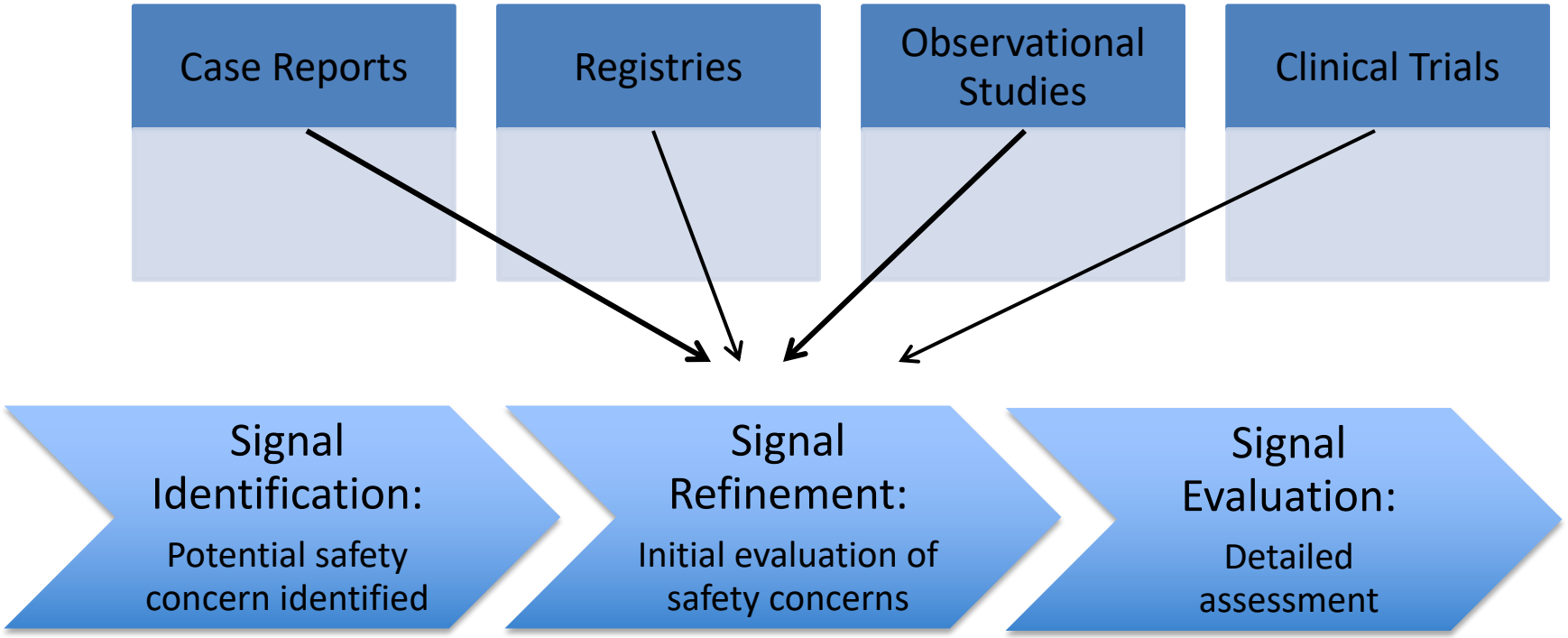
Information from these data sources are used together to provide as complete as possible an understanding of the risk of a drug.

Post-Market Safety Assessment

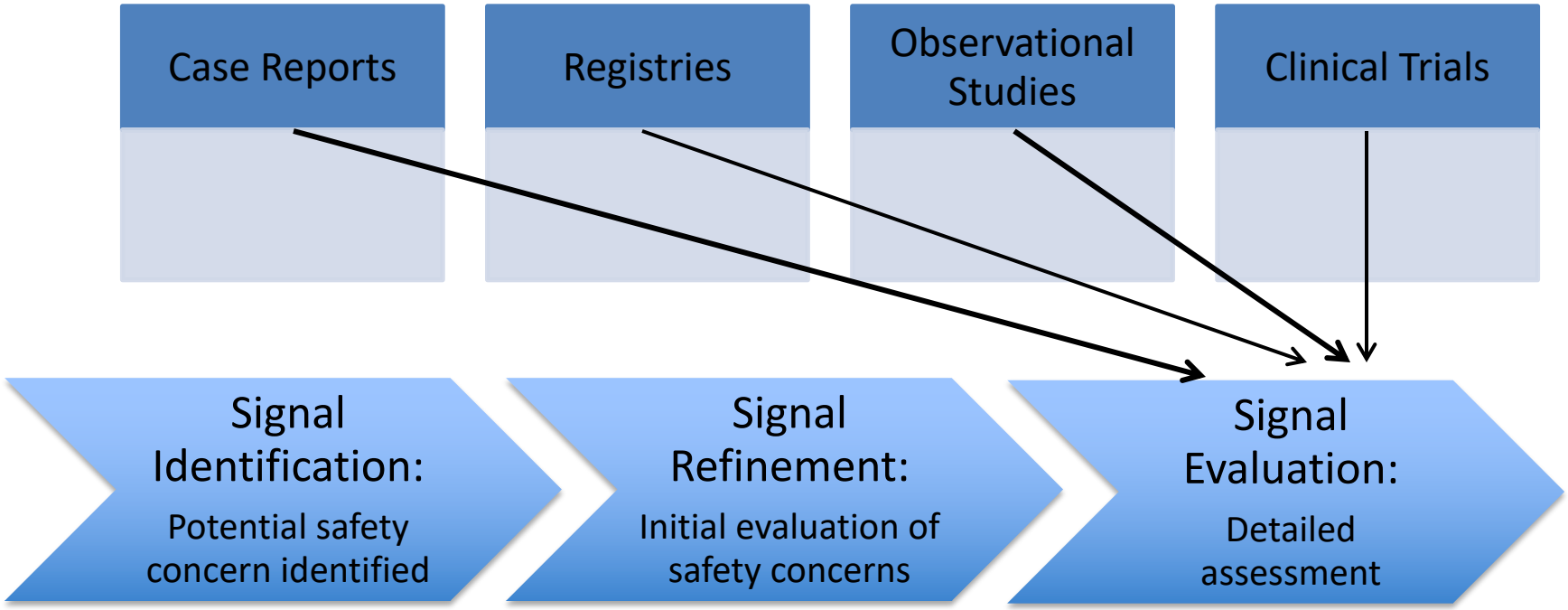
What Gives Rise to Signals at FDA



How We Refine Signals

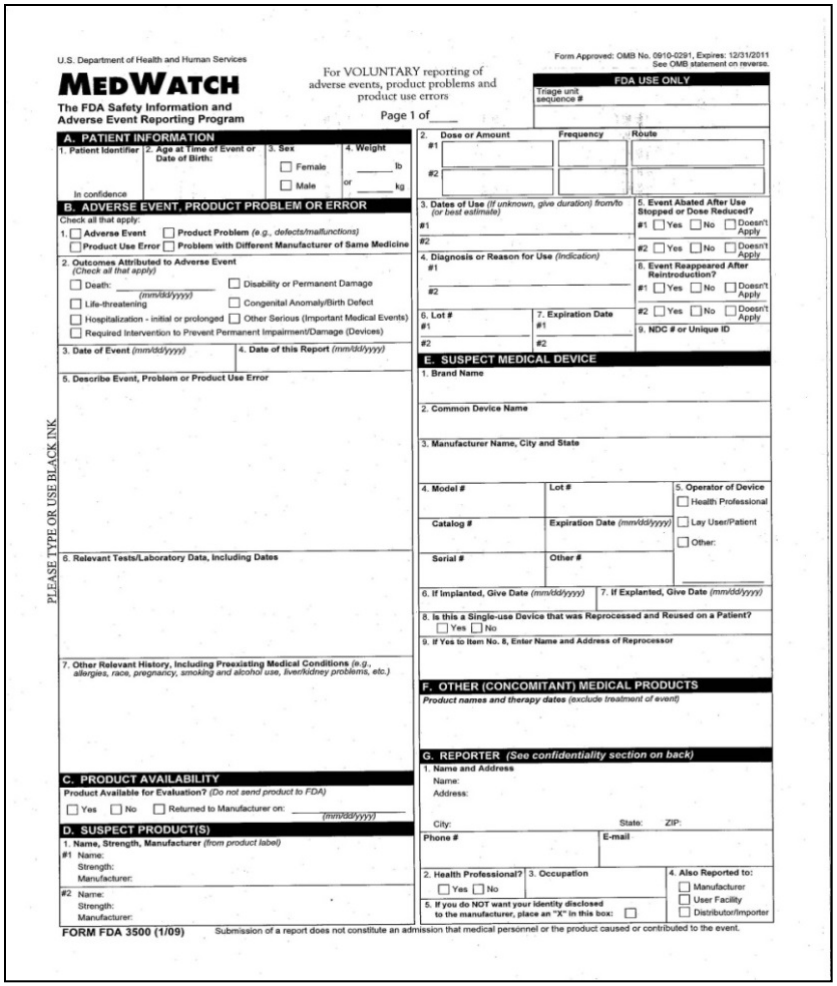


How We Evaluate Signals



Historically….

- Case reports were the main source of drug safety information
  - Good for rare events that are usually the result of drug or toxin exposure
    - Acute liver failure
    - Stevens-Johnson Syndrome
    - Torsades de pointes
- The basis of most drug withdrawals and major safety actions
- However:
  - Often lack critical details
  - Underreporting



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
In confidence
2. Age at Time of Event or Date of Birth:
3. Sex ☐ Female ☐ Male
4. 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: ____ (mm/dd/yyyy) ☐ 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. Dose or Amount | Frequency | Route
#1
#2
3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1
#2
4. Diagnosis or Reason for Use (Indication)
#1
#2
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot #
#1
#2
7. Expiration Date
#1
#2
8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE
1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # | Lot # | 5. Operator of Device ☐ Health Professional
Catalog # | Expiration Date (mm/dd/yyyy) | ☐ Lay User/Patient
Serial # | Other # | ☐ 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
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

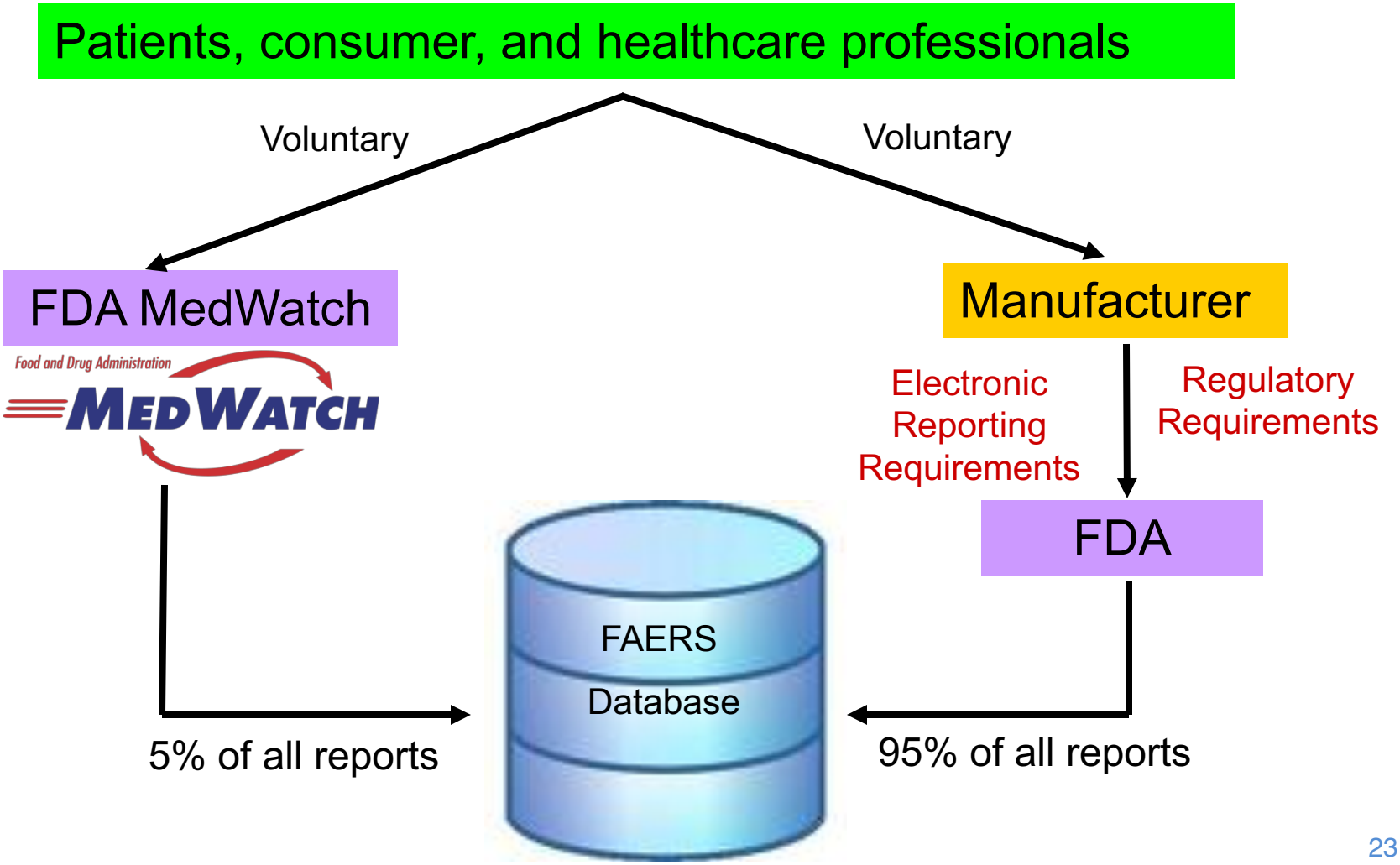
FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Components of a Good Postmarketing Report

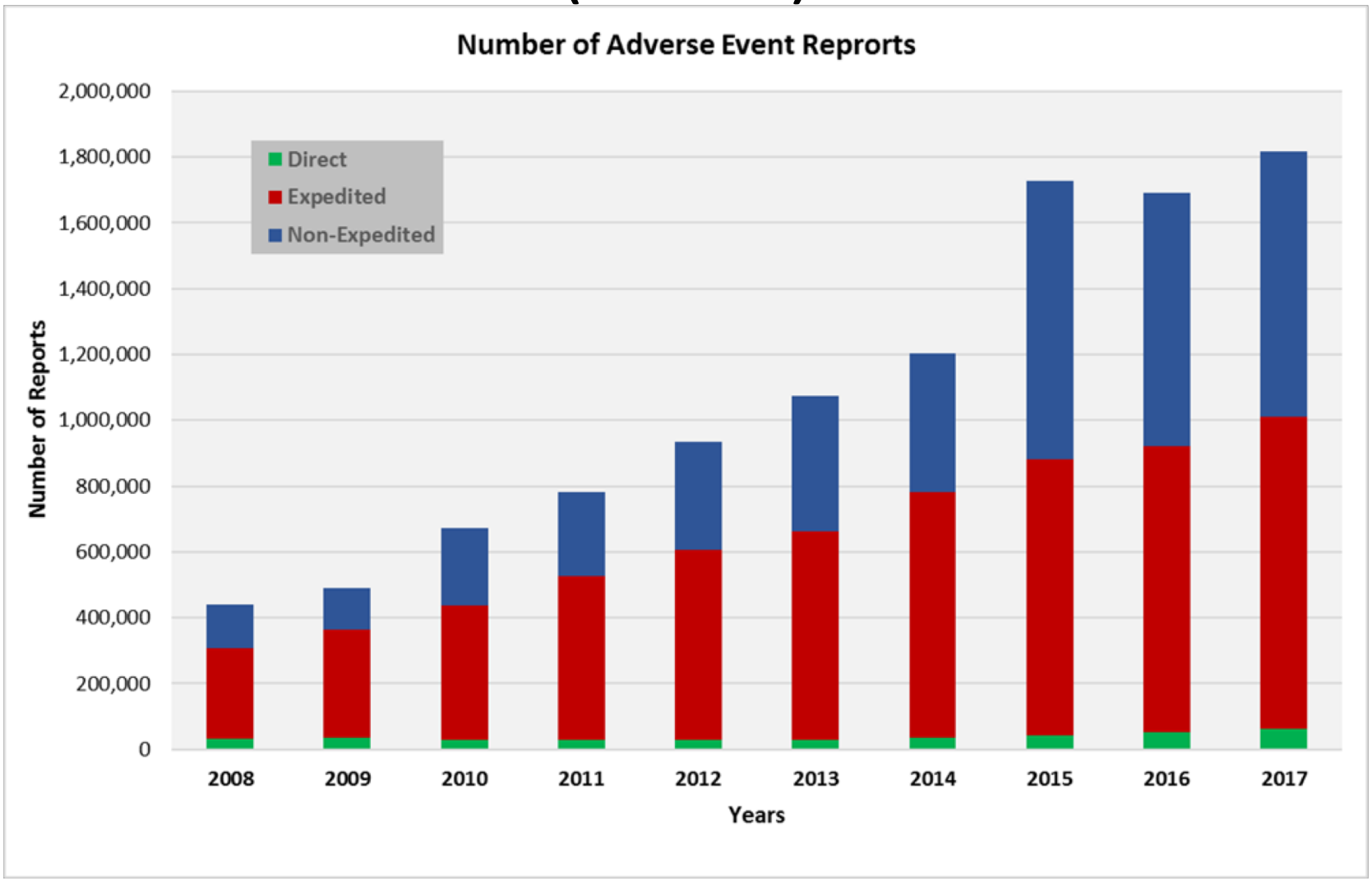
- Description of adverse event
- Identified reporter
- Suspected and concomitant product therapy details (e.g. dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

Source: US FDA. Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005

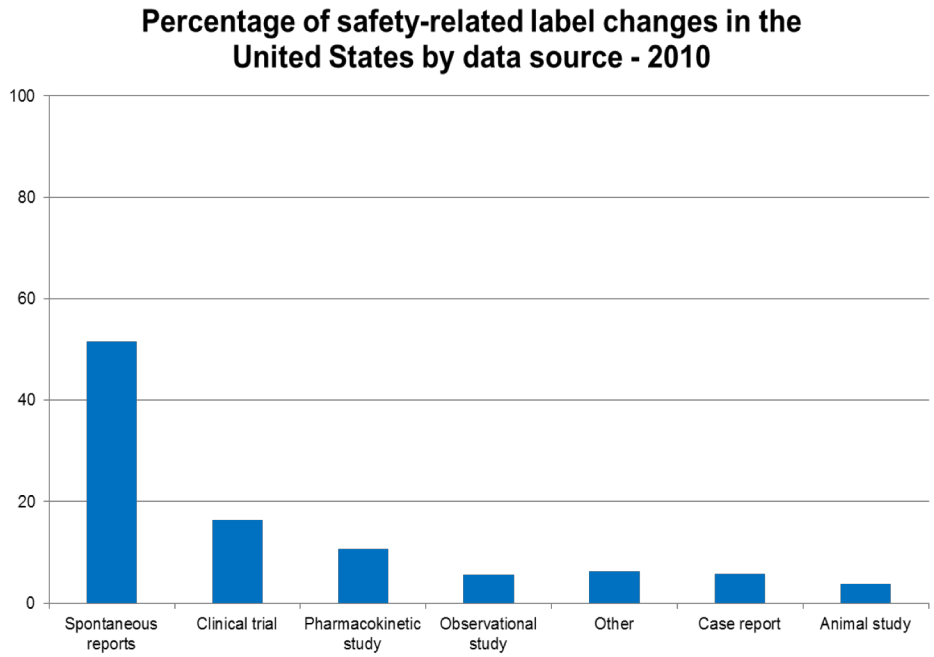
How Postmarketing Reports Get to FDA

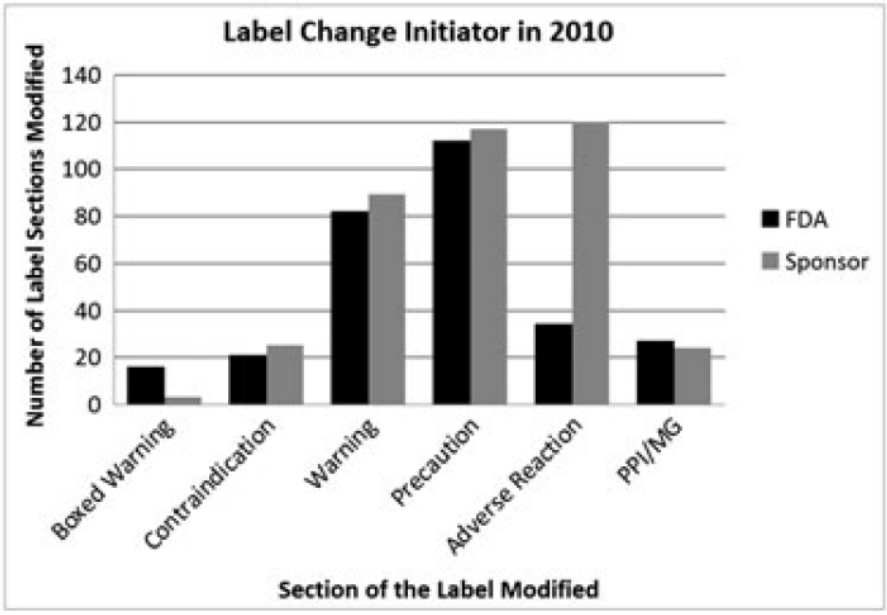


FDA Adverse Event Reporting System (FAERS)



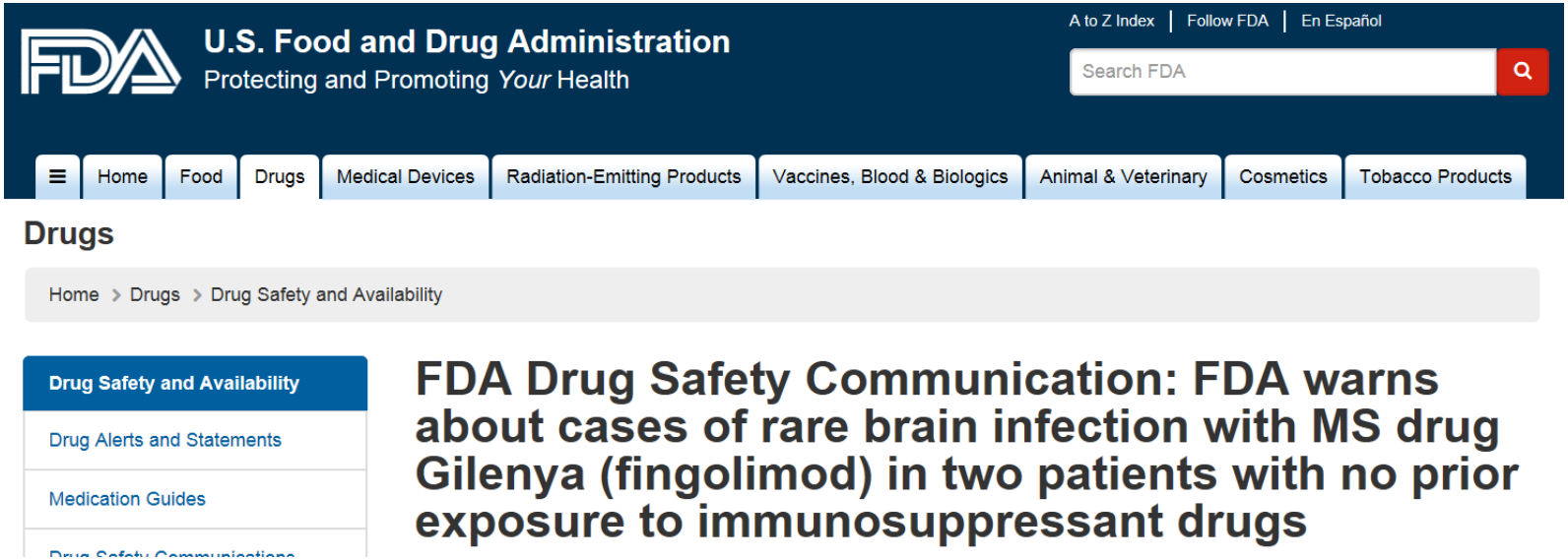
Safety Labeling Changes





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

FDA Action on Fingolomid



[8-4-2015]

Safety Announcement

The U.S. Food and Drug Administration is warning that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking Gilenya (fingolimod) for multiple sclerosis (MS). These are the first cases of PML reported in patients taking Gilenya who had not been previously treated with an immunosuppressant drug for MS or any other medical condition. As a result, information about these recent cases is being added to the drug label.

Source: http://www.fda.gov/Drugs/DrugSafety/ucm456919.htm

Registries

- What is a registry?
  - "Registries are a systematic collection of defined events of product exposures in a defined patient population for a defined period of time."

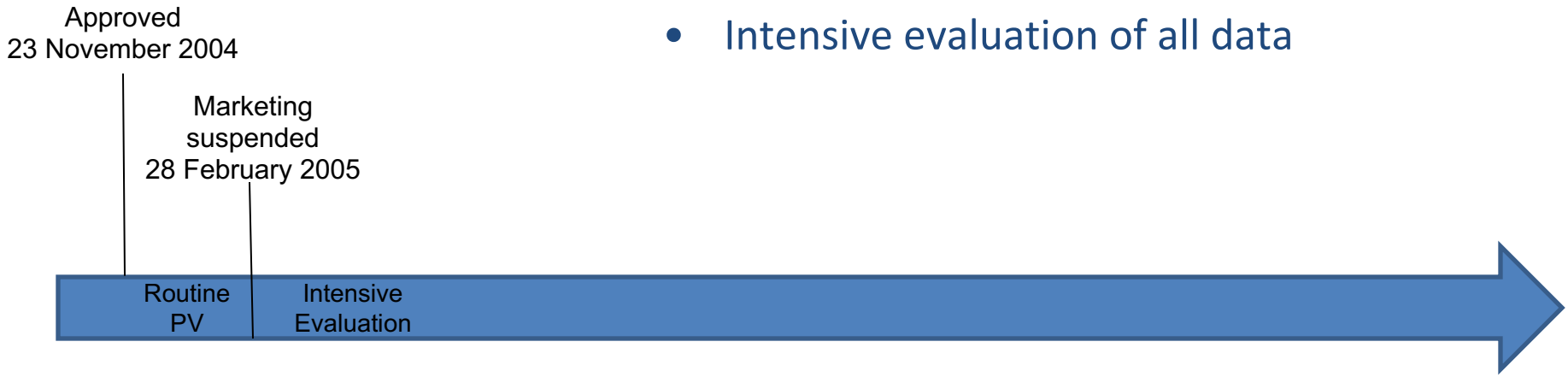
-Strom, *Pharmacoepidemiology*, 4th Ed.

Natalizumab - Approval

- Integrin receptor antagonist
  - Binds to α4-subunit of α4β1 and α4β7 integrins
- Initially approved to reduce frequency of clinical exacerbations in patients with relapsing form of multiple sclerosis
- Routine monitoring in place

Natalizumab – First Cases of PML

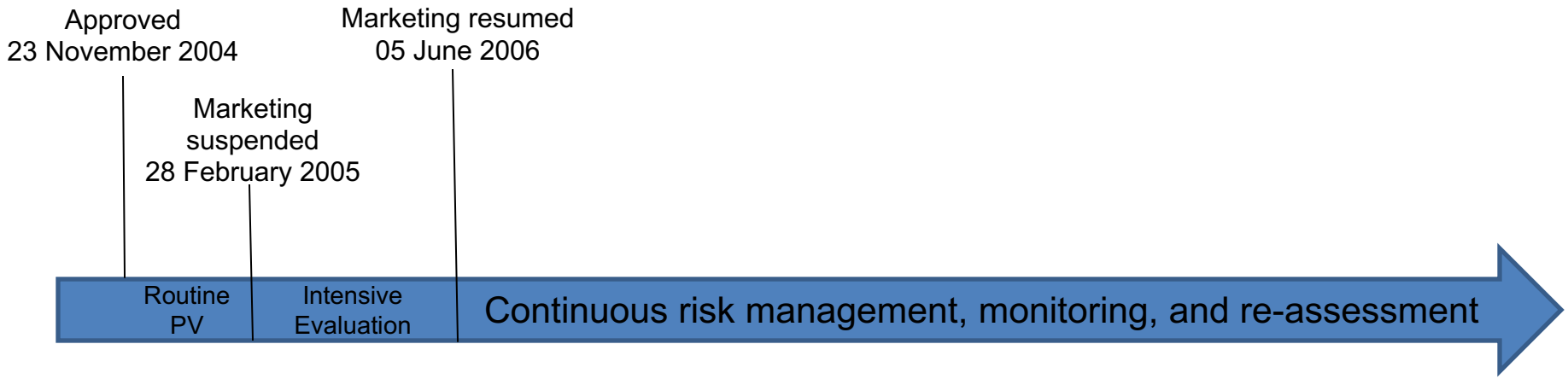
- Within three months of approval, two cases of progressive multifocal leukoencephalopathy (PML) reported in multiple sclerosis patients



- PML is a rare, serious, progressive neurologic disease, usually occurring in immunosuppressed patients, often resulting in irreversible neurologic deterioration and death.
- Marketing was suspended
- Intensive evaluation of all data

Natalizumab – Marketing Resumed

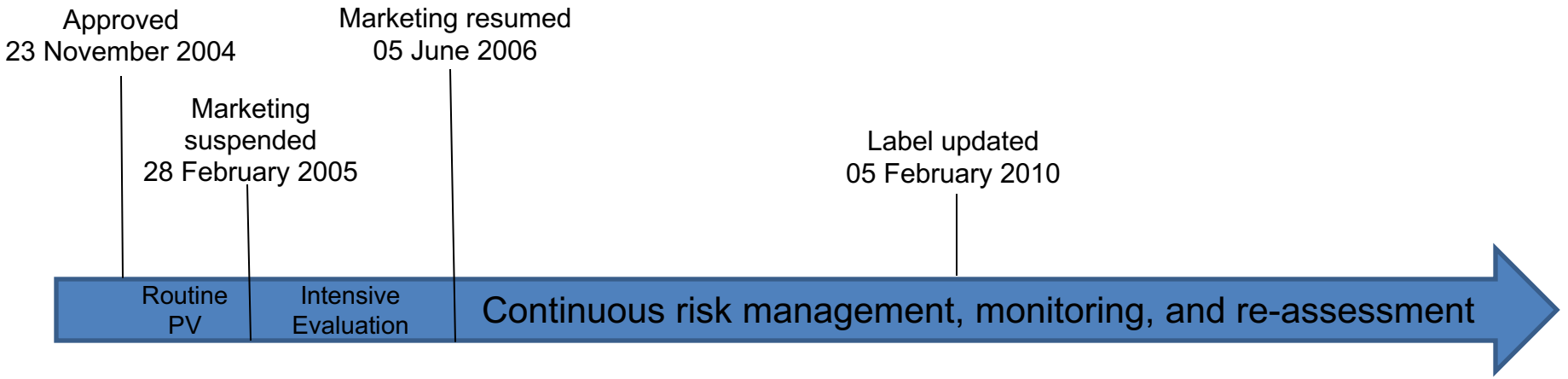
- Intensive evaluation revealed no additional cases in multiple sclerosis patients
- FDA sought input form experts and the public, including patients
- Marketing was resumed with strict risk management
  - Restricted distribution
  - Pre-infusion evaluations
  - Registry of all patients



Natalizumab – Update on Treatment Duration

- Label updated in February 2010 to include duration of treatment as a risk factor for PML
- Based on 31 cases of PML in about 66,000 treated patients

In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunomodulatory therapy. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease.



Natalizumab – Update on Prior Immunosuppression

- Label updated in April 2011 to include prior immunosuppression as a risk factor for PML
- Based on 102 cases of PML in about 82,732 treated patients

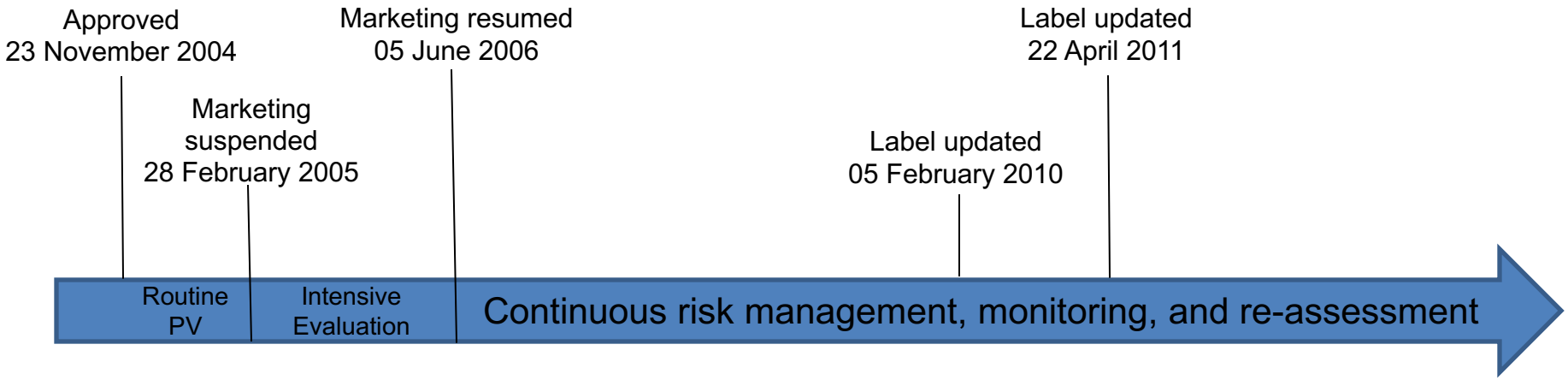
In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunomodulatory therapy. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration.

Table 1: Estimated Incidence of PML in the Postmarketing Setting

Duration of Therapy (Number of Infusions)	PML Incidence per 1,000 Patients
Up to 24	0.3
25-36	1.5
37-48	0.9

†Data as of January 2011
Data beyond 4 years of treatment are limited.

The risk of PML is also increased in patients who have been treated with an immunosuppressant (not including prior treatment with short courses of corticosteroids) prior to receiving TYSABRI.

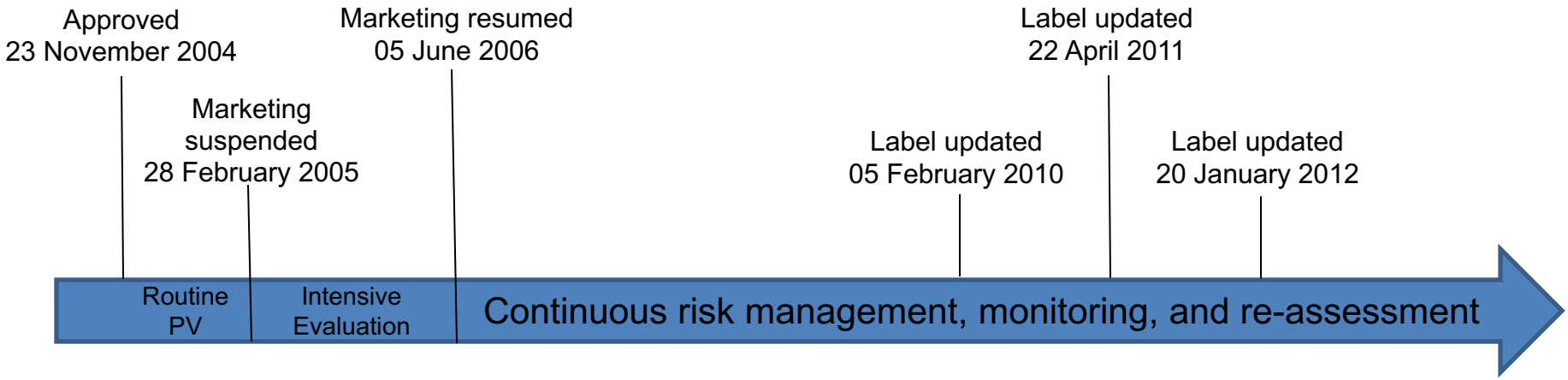


Natalizumab – Update on JC Virus Antibody Positivity

- Label updated in January 2012 to include antibodies to JC virus as a risk factor for PML
- Based on 201 cases of PML in about 96,582 treated patients

In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn's disease patients who were receiving no concomitant immunomodulatory therapy. Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified:

- Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment.
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.



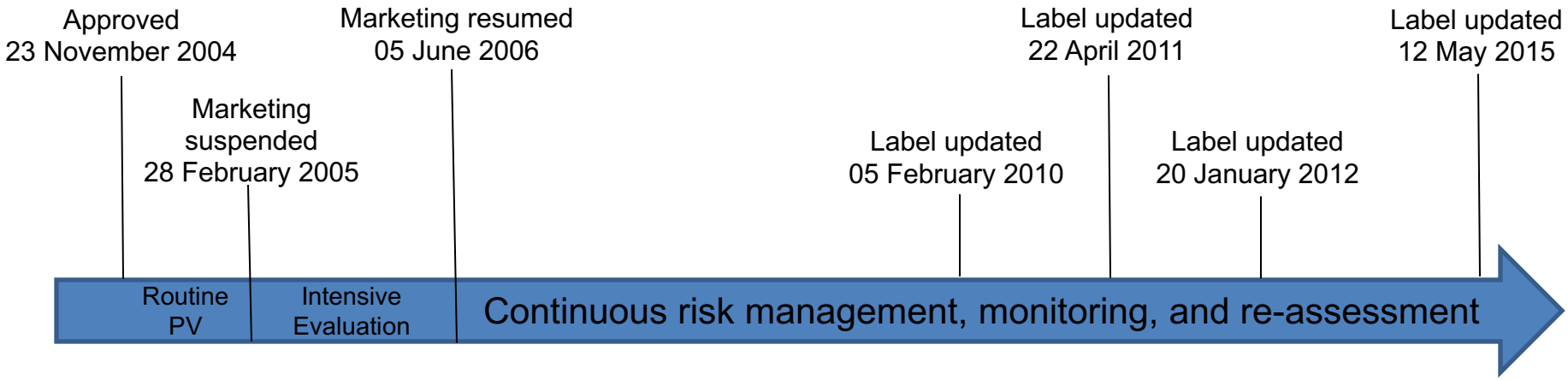
Natalizumab – More Updates

- Label updated in May 2015 to include most recent data on risk factors for PML

Table 1: Estimated United States Incidence of PML Stratified by Risk Factor

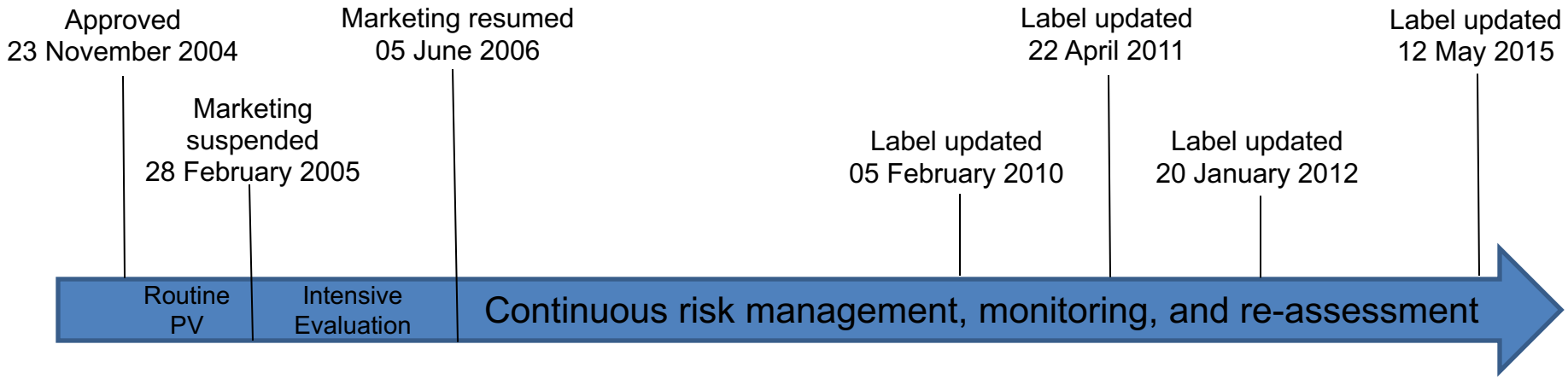
Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<1/1,000	1/1,000
	25-48 months	3/1,000	12/1,000
	49-72 months	6/1,000	13/1,000

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.
†Data beyond 6 years of treatment are limited.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.



Natalizumab – Summary

- Iterative
  - One finding leads to another
- Incremental
  - One step at a time
- Essential
  - Needed for the safe use of the drug



Clinical Trials – An Example

Observational Studies - I

ORIGINAL ARTICLE

Azithromycin and the Risk of Cardiovascular Death

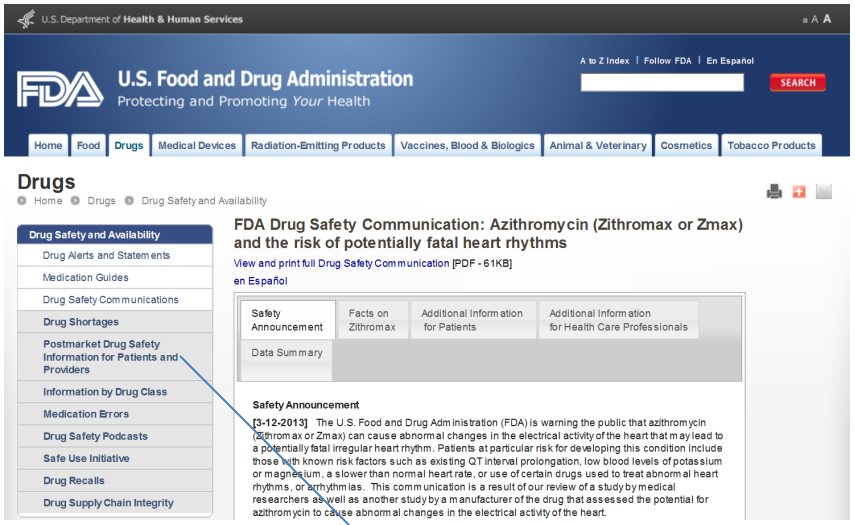
Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

- Retrospective cohort study using Tennessee Medicaid
- Excluded patients at high risk for death from unrelated causes
- Patients who took:
  - Azithromycin (347,795 prescriptions)
  - No antibiotics (1,391,180 prescriptions)
  - Amoxicillin (1,348,672 prescriptions)
  - Ciprofloxacin (264,626 prescriptions)
  - Levofloxacin (193,906 prescriptions)

- Five- and ten-day follow-up periods
- End points :
  - Cardiovascular death
  - Death from any cause
- Propensity-score matching
- Complicated methods
- Lots of careful analyses

Source: Ray WA et al. N Engl J Med 2012;366:1881-90

Observational Studies - II



QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, aminodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Source: US Prescribing Information for Zithromax

- Cardiovascular death:
  - HR = 2.88 (1.79-4.63) (azithromycin vs no antibiotic)
  - HR = 0.95 (0.55-1.63) (amoxicillin vs no antibiotic)
  - HR = 2.49 (1.38-4.50) (azithromycin vs amoxicillin) (Days 1-5)
  - HR = 0.95 (0.44-2.06) (azithromycin vs amoxicillin) (days 6-10)
- Non-cardiovascular death:
  - HR = 0.74 (0.33-1.67) (azithromycin vs no antibiotic)
  - HR = 0.76 (0.42-1.37) (amoxicillin vs no antibiotic)

Source: Ray WA et al. N Engl J Med 2012;366:1881-90

"…there was a small absolute increase in cardiovascular deaths. As compared with amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy; for patients in the highest decile of baseline risk of cardiovascular disease, there were 245 additional cardiovascular deaths per 1 million courses."

Prospective Observational Study

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

*Kimford J Meador, Gus A Baker, Nancy Browning, Morris J Cohen, Rebecca L Bromley, Jill Clayton-Smith, Laura A Kalayjian, Andres Kanner, Joyce D Liporace, Page B Pennell, Michael Privitera, David W Loring, for the NEAD Study Group**

Lancet Neurol 2013; 12: 244–52
Published Online
January 23, 2013
http://dx.doi.org/10.1016/

Summary

Background Many women of childbearing potential take antiepileptic drugs, but the cognitive effects of fetal exposure are uncertain. We aimed to assess effects of commonly used antiepileptic drugs on cognitive outcomes in children up to 6 years of age.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total-enrolled				
Participants	94 (30%)	100 (32%)	55 (18%)	62 (20%)
Mean IQ*	105 (102–108)	108 (105–110)	108 (104–112)	97 (94–101)
Difference	7 (3–12)	10 (6–15)	10 (5–16)	NA
p value†	0·0015	0·0003	0·0006	NA
Age-6-completers				
Participants	61 (27%)	74 (33%)	40 (18%)	49 (22%)
Mean IQ*	106 (103–109)	108 (105–111)	109 (105–113)	98 (95–102)
Difference	8 (3–13)	10 (6–15)	11 (5–16)	NA
p value†	0·0010	0·0003	0·0004	NA

Data are n (%) or n (95% CI), unless otherwise stated. IQ=intelligence quotient. NA=not applicable. *Mean IQ scores at age 6 years were adjusted for maternal IQ, dose, periconceptional folate, and gestational age at delivery; total-enrolled analysis includes imputed IQ data; unadjusted means for the total-enrolled analysis were carbamazepine 105, lamotrigine 109, phenytoin 103, and valproate 98, and unadjusted means for age-6-completers were carbamazepine 106, lamotrigine 110, phenytoin 105, and valproate 98. †p values were adjusted for three pairwise comparisons to valproate with Hochberg's correction.

Table 2: **Differences from valproate in mean IQ scores in all children in the study (n=311) and in children at 6 years of age (n=224)**

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Depakote safely and effectively. See full prescribing information for Depakote.

Depakote (divalproex sodium) tablets, for oral use
Initial U.S. Approval: 1983

WARNINGS: LIFE THREATENING ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

- **Hepatotoxicity, including fatalities, usually during the first 6 months of treatment. Children under the age of two years and patients with mitochondrial disorders are at higher risk. Monitor patients closely, and perform serum liver testing prior to therapy and at frequent intervals thereafter (5.1)**
- **Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ (5.2, 5.3, 5.4)**
- **Pancreatitis, including fatal hemorrhagic cases (5.5)**

Real-world Evidence

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

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

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P.,
Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H.,
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).

Moving Forward

PERSPECTIVES

COMMENTARY

The FDA's Sentinel Initiative—A Comprehensive Approach to Medical Product Surveillance

R Ball[1], M Robb[1], SA Anderson[2] and G Dal Pan[1]

In May 2008, the Department of Health and Human Services announced the launch of the Sentinel Initiative by the US Food and Drug Administration (FDA) to create the Sentinel System, a national electronic system for medical product safety surveillance.[1,2] This system complements existing FDA surveillance capabilities that track adverse events reported after the use of FDA regulated products by allowing the FDA to proactively assess the safety of these products.

distributed-data approach; (3) successful development of processes for turning safety concerns into queries of the Mini-Sentinel data; and (4) making good progress toward building a mature data analytics system.[5] Other major accomplishments included exceeding the FDAAA 2007 milestones with over 300 million person-years of high quality, unduplicated, curated data and recruiting a broad group of scientific collaborators who regularly provide the FDA with valuable technical support in evaluating electronic health data.[6] The report also points out that although the FDA has reported using Mini-Sentinel information in only a few cases (Table 2), Mini-Sentinel information has provided supporting information in many other situations, including when the information shows that existing FDA labels and communications are

Sentinel data are collected for multiple purposes

Administrative Data

- Collected for transactional recordkeeping, reimbursement

Clinical Data

- Collected to document elements of clinical care and support physician decision-making

Registries

- Collected to provide information on a specific population of interest

Sentinel uses data and expertise from multiple sources

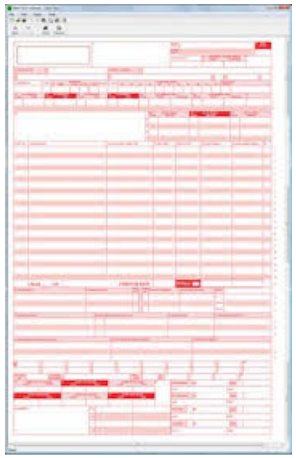
Lead – HPHC Institute

Data and scientific partners

Scientific partners

Data partners have varied source systems

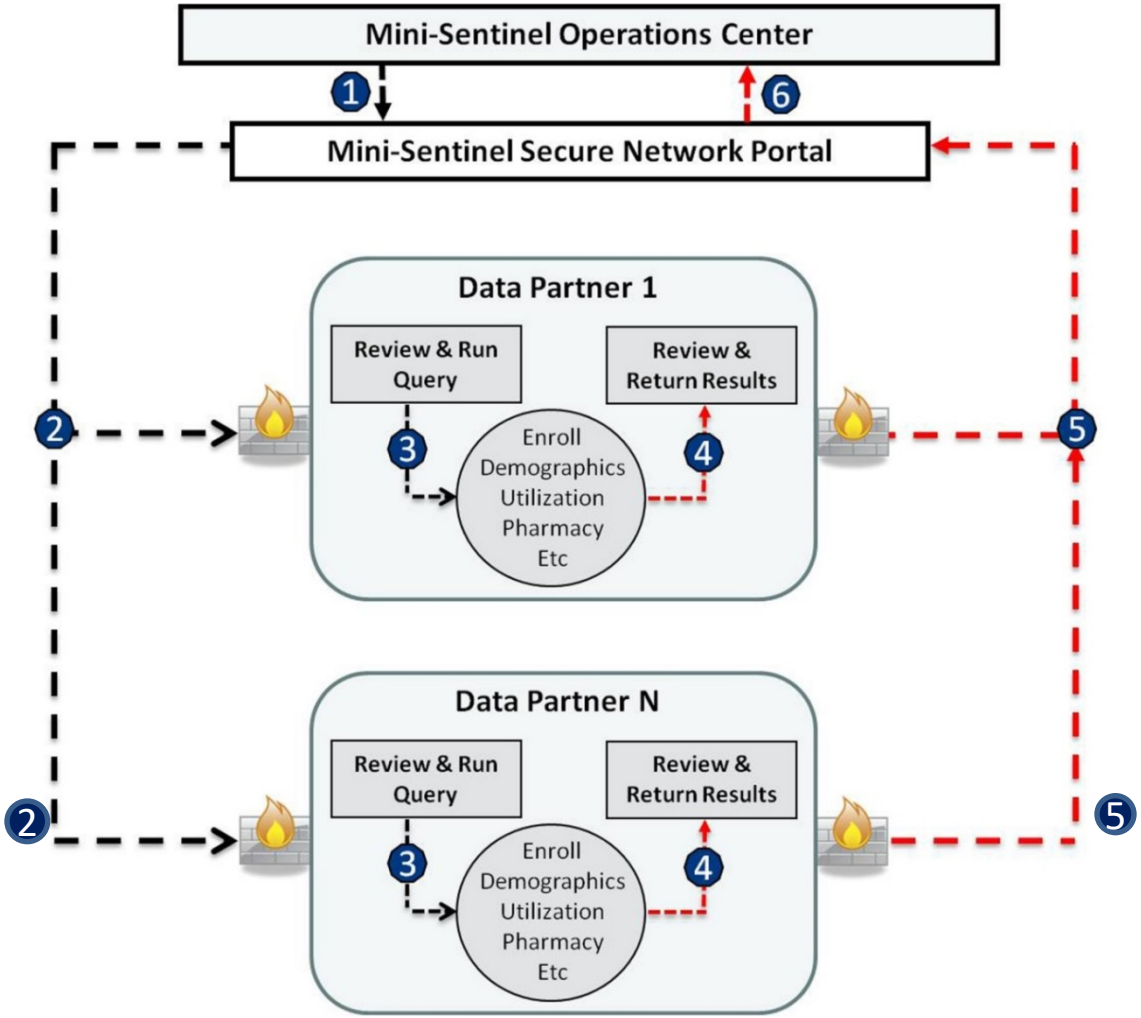
Claims-based Systems
(7 Partners; ~90% of members)



Integrated Delivery Systems
(10 Partners; ~10% of members)

Stand-alone EHR
(1 Partner; 50M encounters)

Analysis in Sentinel's distributed data network



1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

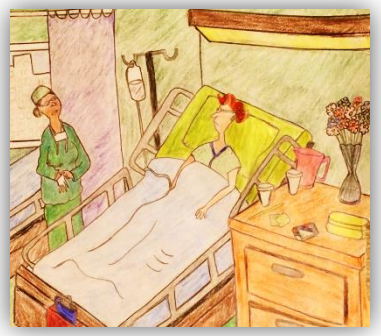
5- Data partners return results via secure network

6- Results are aggregated

Bob's Story

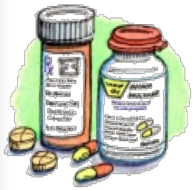
Demographic				
Coverage	**PatID**	**Birth Date**	**Sex/Race**	**Zip**
Harvard Pilgrim Health Care	5291321	07/29/63	M/Unknown	02119

Lives in Boston, MA



Has appendectomy

Diagnosed with hypertension



Routine Office Visit

Encounter

- 1/1/2011
  Office Visit
- **Dx:** Influenza with pneumonia

Dispensings

- 1/1/2011
- **Rx:** Antibiotic

Encounters

- 3/15/2012
  Emergency Department
- **Px:** appendectomy

- 3/15/2012-3/18/2012
  Hospital
  Inpatient stay

Encounter

- 12/11/12
  Office Visit
- **Dx:** Hypertension

Dispensings

- 12/11/12
- **Rx:** Anti-hypertensive

Encounter

- 10/31/13
  Office Visit
- **Dx:** Hypertension

Bob is a 47-50 year old male with 1,035 days of observed time

2011 2012 2013 2014

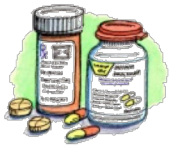
Bob's Story

Gets new job in San Jose, CA

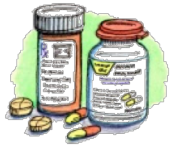
Bob's Story

Demographic				
Coverage	**PatID**	**Birth Date**	**Sex/Race**	**Zip**
KAISER PERMANENTE	5678910	07/29/63	M/White	95192

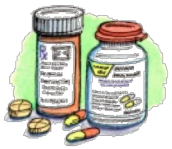
Routine Office Visit



Diagnosed with anxiety



Has stroke in Los Gatos, CA



Encounter	Dispensing	Encounter	Dispensing	Test Results	Encounter	Dispensing
• 11/01/2013 **Office Visit** • **Dx:** Hypertension	• 11/01/2013 • **Rx:** Anti-hypertensive	• 01/09/2014 **Office Visit** • Dx: Hypertension • Dx: Anxiety • Dx: Ankle sprain	• 01/09/2014 • **Rx:** Antianxiety	• 01/09/2014 • **A1C & Glucose** • ***(EHR data at Kaiser)***	• 02/14/2015 • **Emergency Department** • 02/15/2015- • 02/20/2015 • **Hospital**	• 2/20/2015 • **Rx:** Platelet inhibitor

Bob is a 50-52 year old white male with 640 days of observed time

2013 2014 2015 2016

FDA Experience with RWD/RWE

425 million person years of observation time
43 million people currently accruing new data
5.9 billion pharmacy dispensings
7.2 billion unique medical encounters
42 million people with at least one laboratory test result

Network of Collaborators

Sentinel brings together public, academic and private organizations that provide access to healthcare data and expertise.

Data at a Glance

The Sentinel Distributed Database is comprised of quality-checked electronic data held by 18 partner organizations.

Statistical Methods

Sentinel explores the application of a wide range of methods to enhance medical product safety assessment.

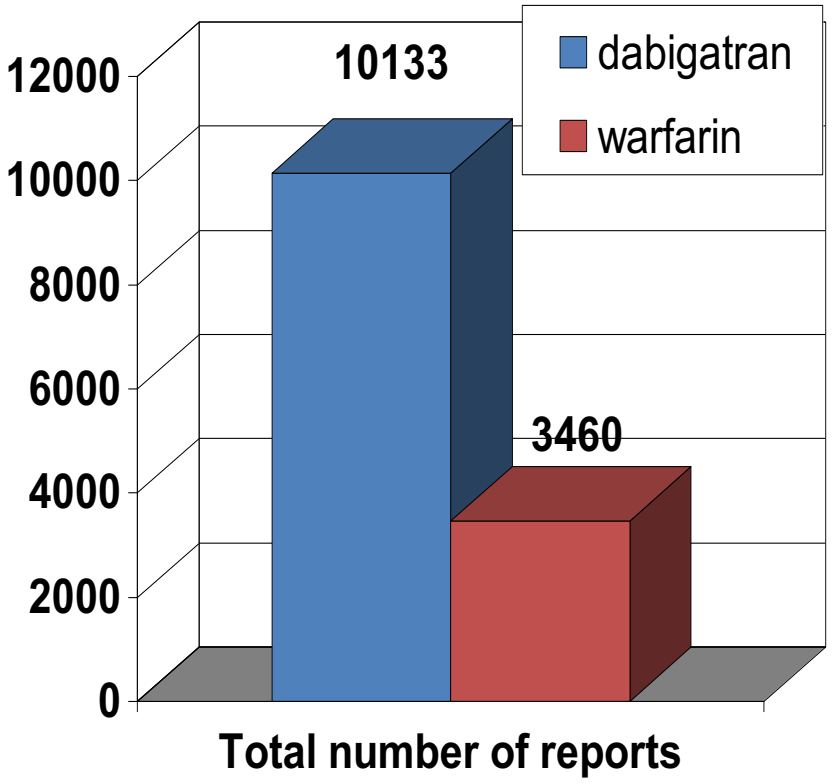
https://www.sentinelinitiative.org/

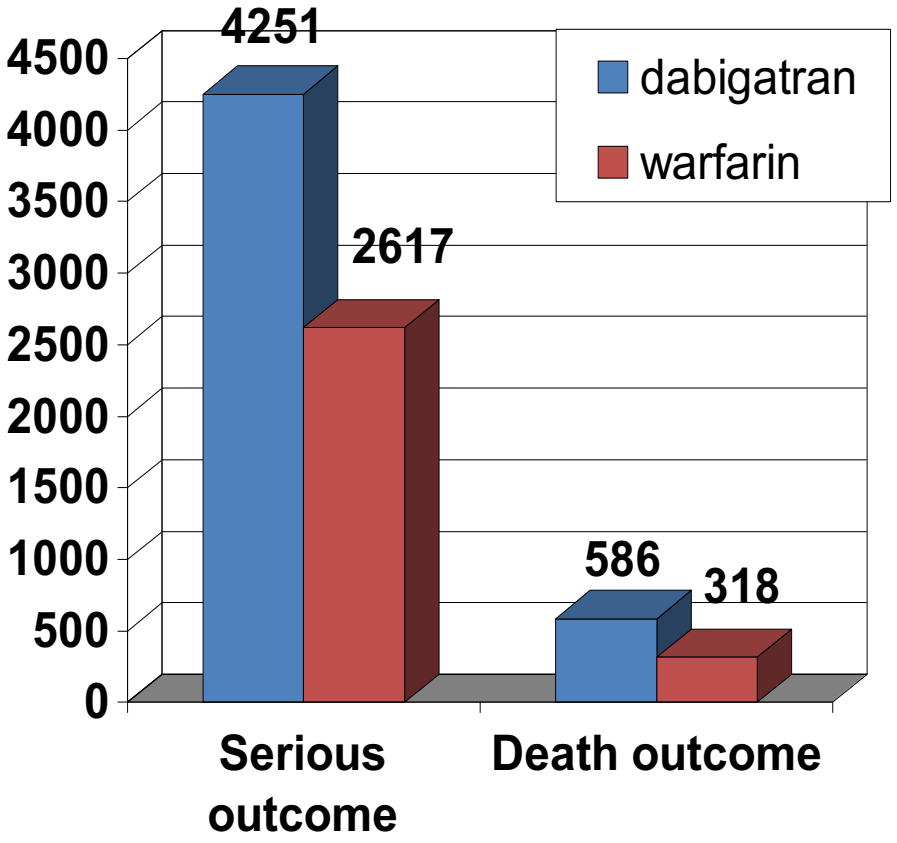
Dabigatran and Bleeding Complications

- Approved October 19, 2010 indication of non-valvular atrial fibrillation
- Anticipating a protocol based assessment in Mini-Sentinel at time of approval
- Large number of spontaneous adverse event reports
  - A large number of reports is expected for drugs new to the market compared to other drugs on the market for many years
  - Determine if we could use rapid query in Mini-Sentinel to put a potential bound on risk
- Modular program feature of Mini-Sentinel

Challenges with Large Number of Case Reports

FAERS Reports with Dabigatran and Warfarin: October 19 2010 - October 5, 2011



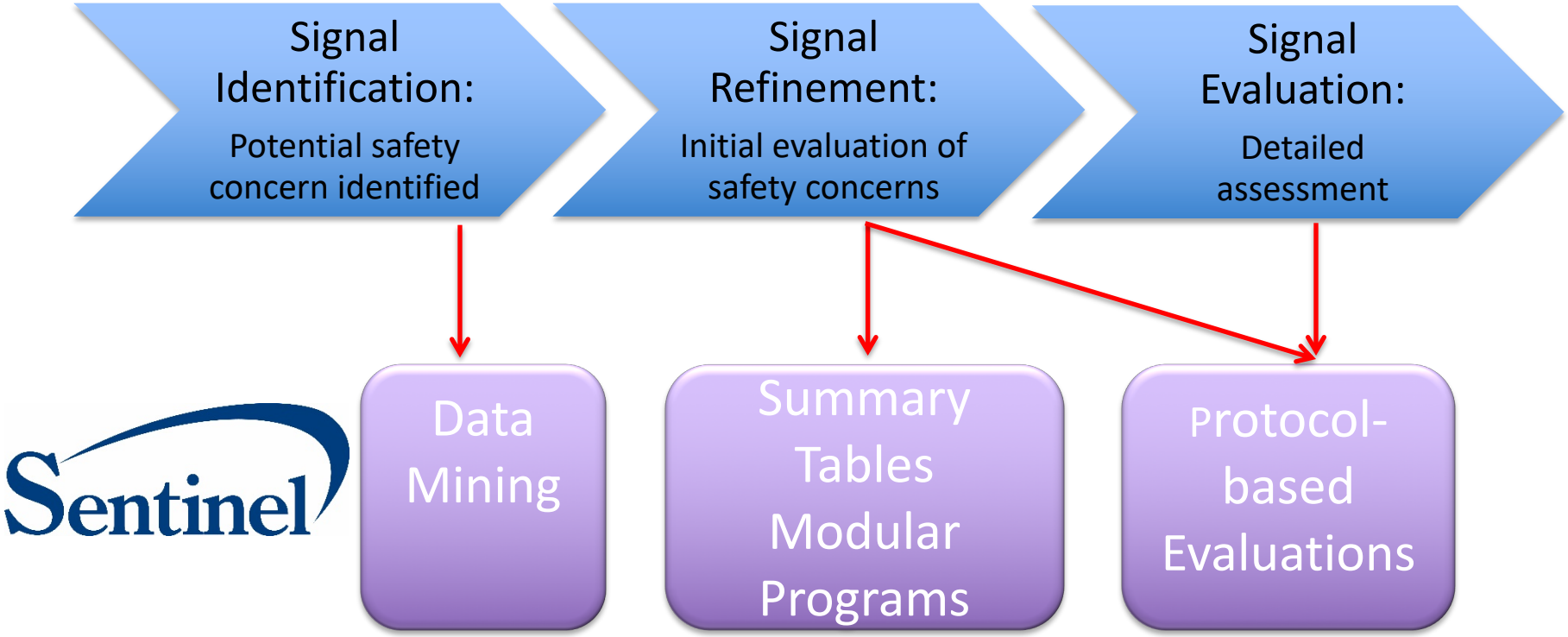


Intracranial (ICH) and Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel

(Oct 2010 – Dec 2011, Incidence Rate =New Events/100,000 Days at Risk)

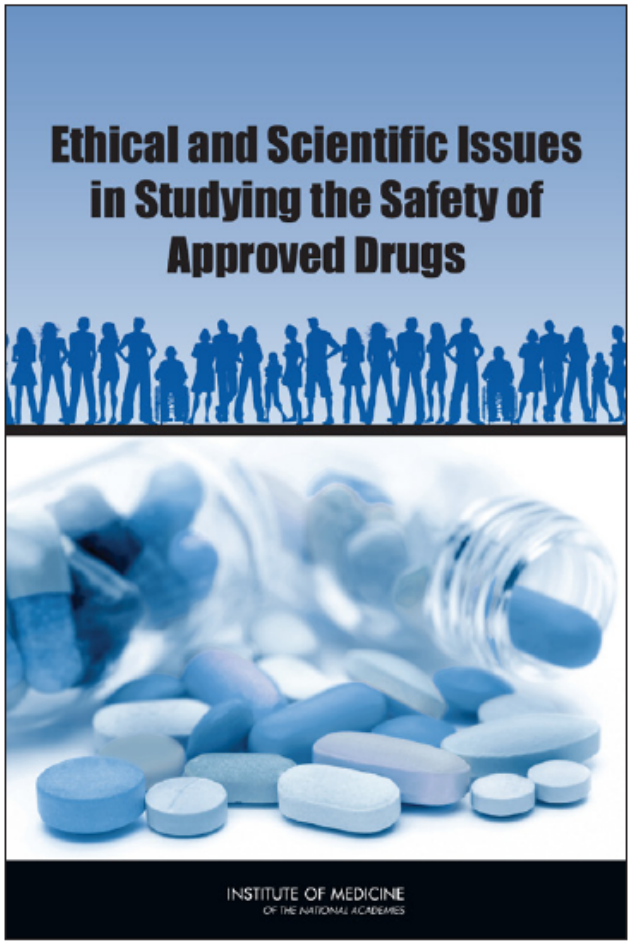
Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,569	2.2	Atrial Fibrillation – 183 days	43,351	5.8
9,216	2.2	Atrial Fibrillation – 365 days	34,800	6.1
12,161	2.4	No requirement – 183 days	119,470	5.0
10,464	2.5	No requirement – 365 days	97,267	5.2

Post-Market Safety Assessment

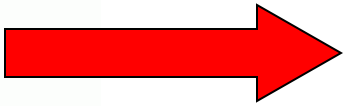


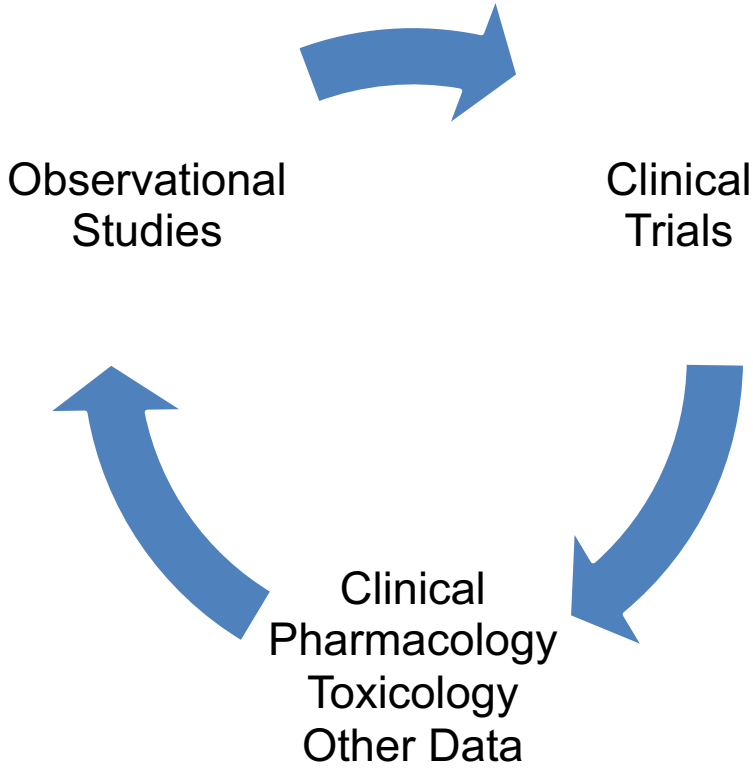
Current Challenges

- Deciding what questions need to be answered
- Deciding the best way to answer them
- Understanding the trade-offs in various approaches
- Ethical considerations
- Communications
- Regulatory actions

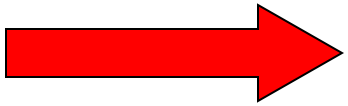


From Traditional Hierarchy to Synthesis of Evidence





Traditional hierarchy



Synthesis of evidence

Thank you


FDA
U.S. FOOD & DRUG
ADMINISTRATION