Emerging Regulatory Changes in Post-Approval Safety and Risk Management

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The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

No conflicts of interest to disclose

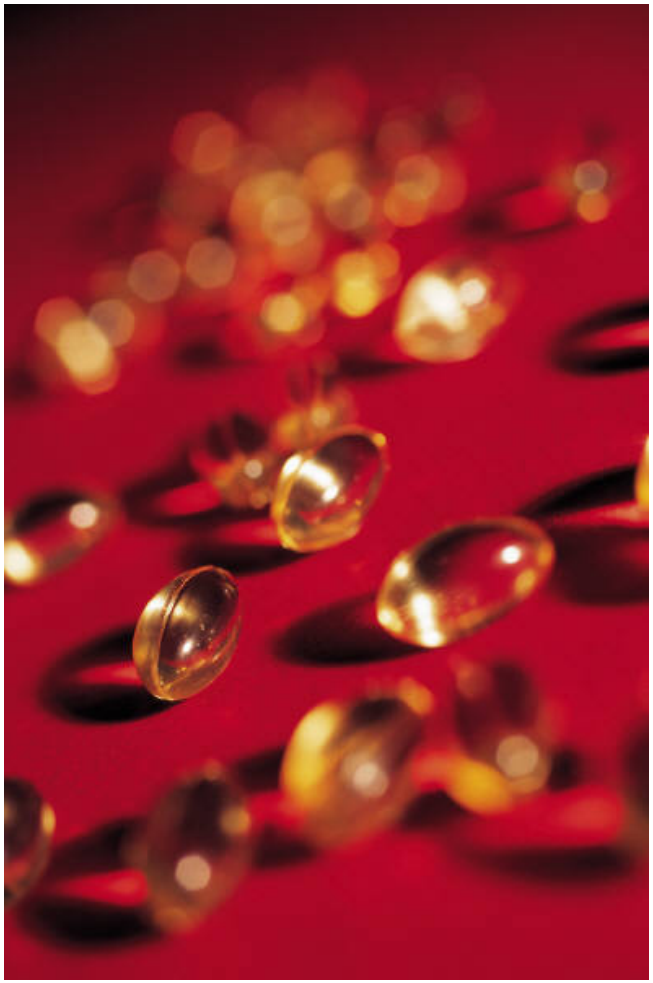
Overview

- Some recent trends
- Adverse event reporting
- Epidemiological studies and clinical trials
- Risk management
- Summary of selected FDAAA activities
- Risk communication
- Looking to the future

Some Recent Trends

Goals of Drug Safety Surveillance

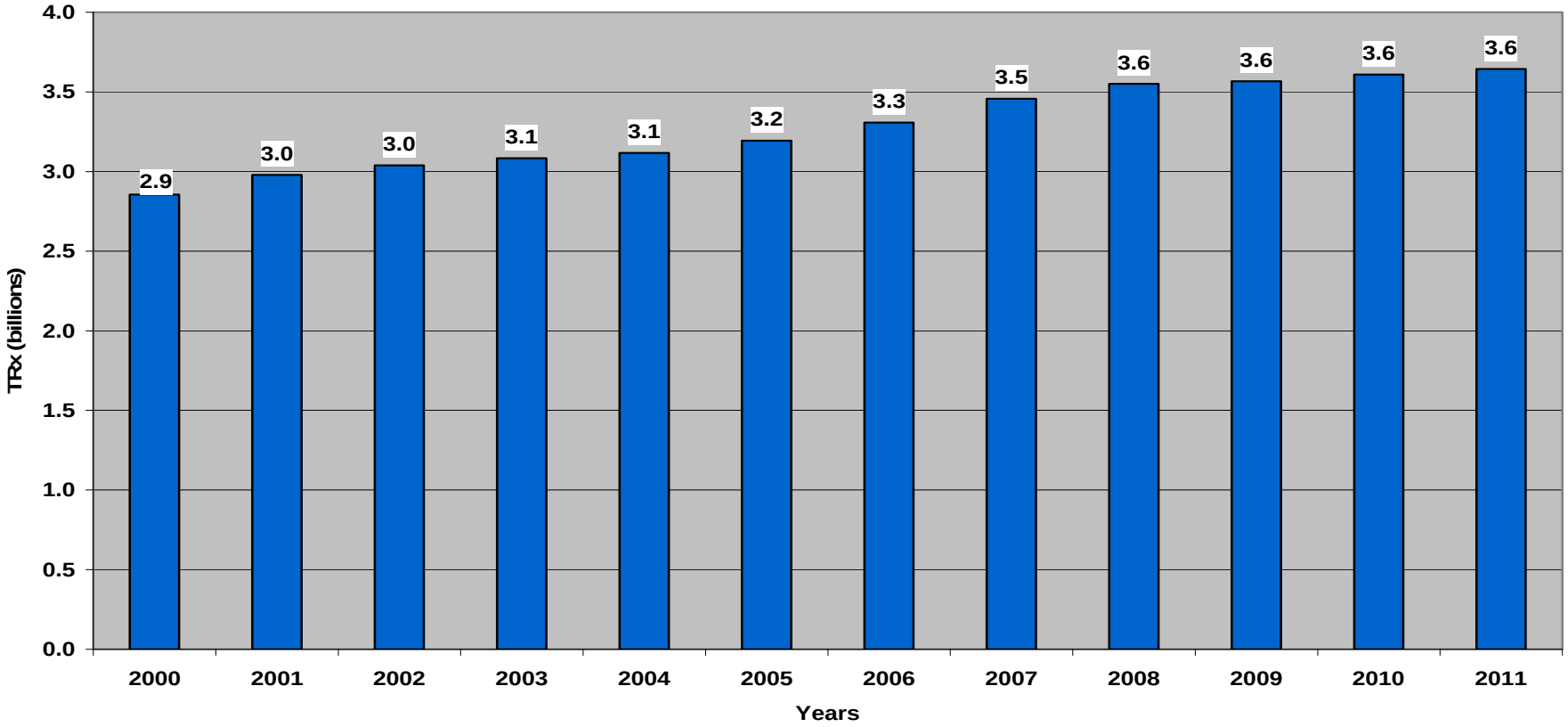
- To identify previously unknown drug-related adverse events
- To learn more about known drug-related adverse events
- To learn more about how drugs are used in ways that may not promote safe use
- The method you use depends on what you are trying to learn
- To communicate findings about drug safety



Growing Volume of Medication Usage - US

Total number of prescriptions dispensed from U.S. outpatient retail pharmacies, Years 2000 - 2011

Source: IMS Health, Vector One®: National. Extracted March 2012



Why Drugs Are Withdrawn

- Torsade de Pointes
  - Mibefradil (1998)
  - Terfenadine (1998)
  - Astemizole (1999)
  - Grepafloxacin (1999)
  - Cisapride (2000)
  - Levacetyl methadol (2003)
  - Propoxyphene (2010)

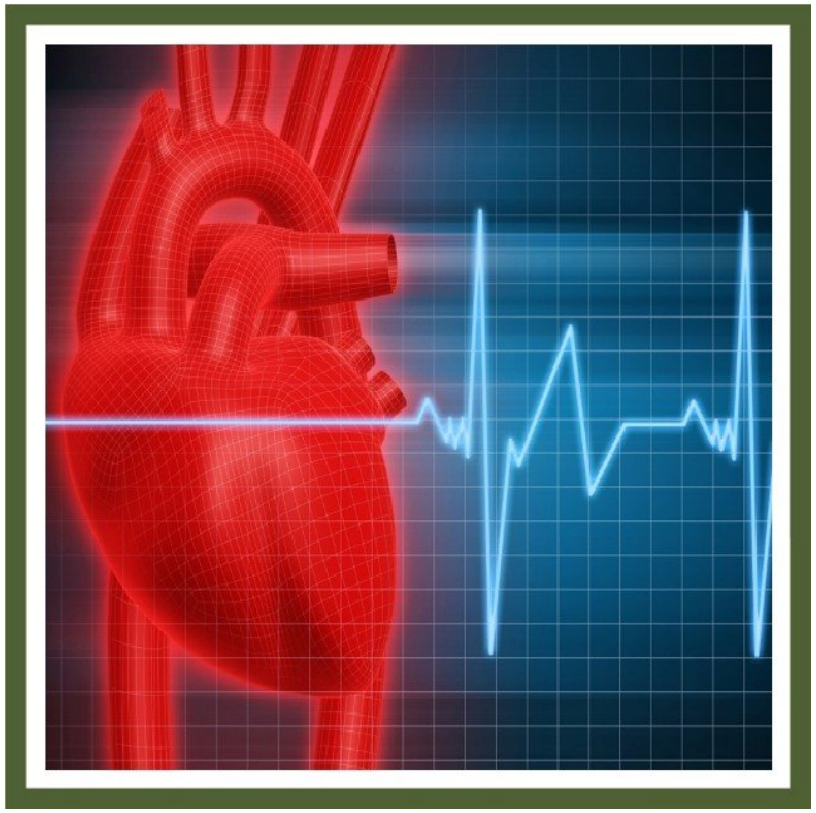
- Other Cardiovascular:
  - Pergolide - valvulopathy (2007)
  - Fenfluramine - valvulopathy (1997)
  - Rofecoxib (2004) – AMI
  - Sibutramine (2010) - CV events
  - Tegaserod (2007) – CV events
  - Azaribine – arterial thrombosis (1976)
  - Encainide – Mortality (1991)
  - Phenylpropanolamine – hemorrhagic stroke (2000)

- Drug-induced Liver Disease:
  - Ticrynafen (1980)
  - Benaxoprofen (1982)
  - Bromfenac (1998)
  - Trovafloxacin (1998, returned to market)
  - Troglitazone (2000)
  - Pemoline (2005)

- Other:
  - Natalizumab – PML (2005, returned to market)
  - Zomepirac – anaphylaxis (1983)
  - Suprofen – Acute renal failure (1987)
  - Etretinate – birth defects (2002)
  - Rapacuronium – bronchospasm (2001)
  - Temofloxacin – hemolysis, renal failure (1992)
  - Nomifensine – hemolytic anemia (1986)
  - Gatifloxacin (non-ophthalmic) – hyper- and hypoglycemia (2006)
  - Aprotinin – increased mortality (2007)
  - Alosetran – ischemic colitis (2000, returned to market)
  - Phenformin – lactic acidosis (1978)
  - Flosequinan – increased mortality (1993)
  - Methaqualone – overdose (1984)
  - Cerivastatin – rhabdomyolysis (2001)
  - Valdecoxib – Stevens-Johnson syndrome (2005)

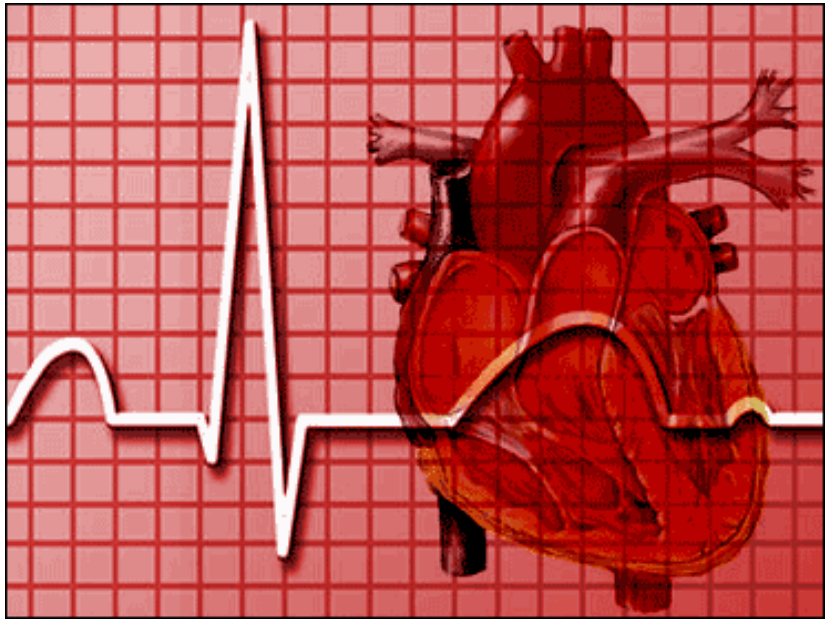
Why Adverse Cardiovascular Effects of Medicines are Important

- Cardiovascular disease is highly prevalent in our society
- Many drug affect the cardiovascular system
- Sorting our drug effect from the background prevalence is quite complicated



Cardiovascular-related Drug Safety Communications - 2011

- Rosiglitazone
  - CV risk
- Abacavir
  - MI
- Lopinavir
  - Congential cardiac abnormalities
- Olmesartan
  - CV events
- Drosperinone
  - VTE/ATE
- Varenicline
  - CV events
- Dronedarone
  - Increased mortality and CV events
- Citalopram
  - Torsade/Prolonged QT at high doses
- Odansetron
  - QT prolongation
- ADHD drugs
  - CV events
- SSRIs
  - persistent pulmonary hypertension of the newborn



Historically….

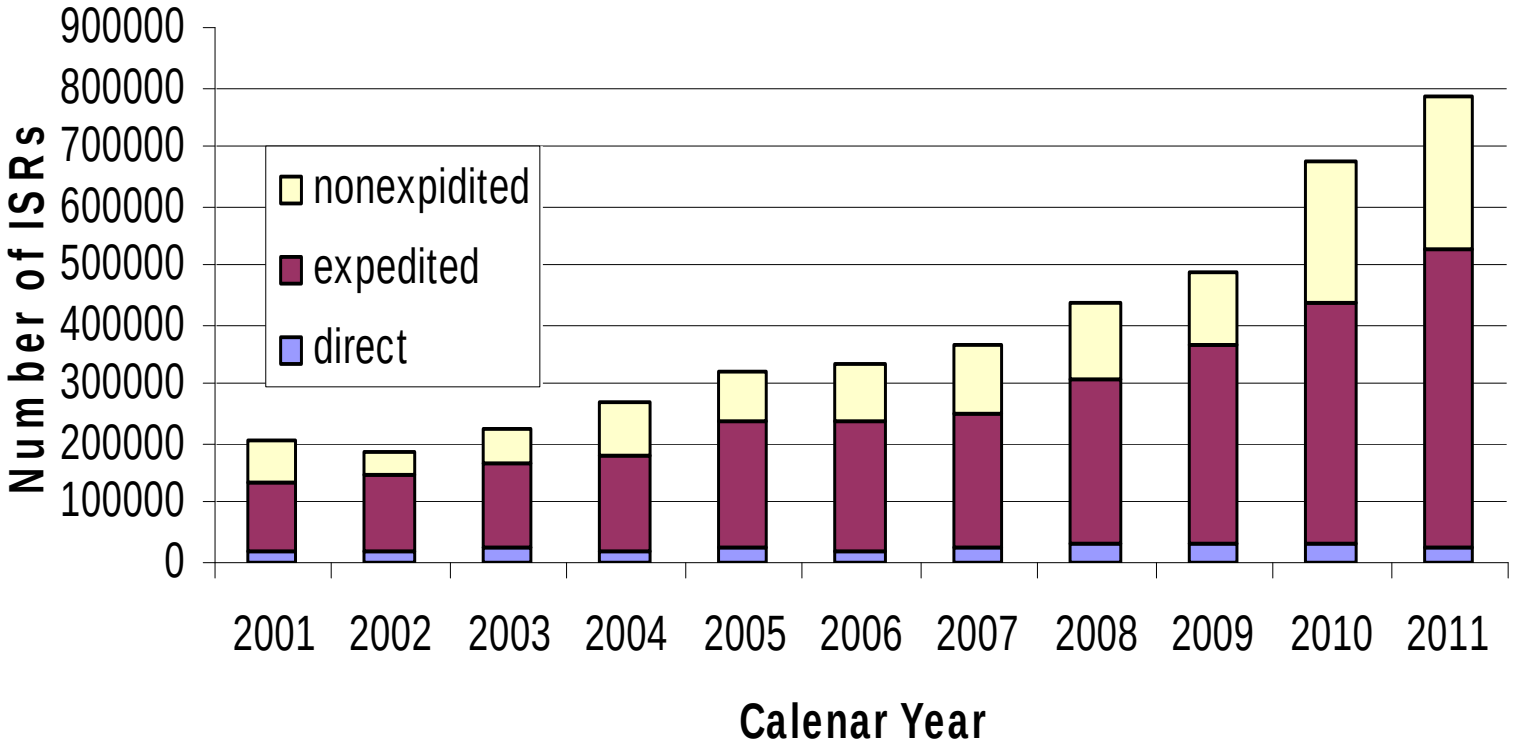
- Individual case safety reports were the main source of drug safety information
  - Good for rare events that are usually the result of drug or toxin exposure
    - Acute liver failure
    - Stevens-Johnson Syndrome
    - Torsades de pointes
- Most drug withdrawals and major safety actions arerelated to one of these events

Today….

- Large databases are available for drug safety studies
- We can detect much more subtle adverse drug effects including increases in relatively common events
  - Common in the population
  - Manifestation of the disease being treated

Adverse Event Reporting

Growing Number of Adverse Event Reports - US



Qualities of a Good Case Report

- What makes a good case report?
  - Description of the event
  - Suspected product(s) and concomitant treatment details
  - Patient characteristics, medical history, treatment history
  - Documentation of the diagnosis
  - Clinical course and outcomes
  - Treatment and lab values at baseline, during therapy, and after therapy
  - Response to dechallenge and rechallenge
  - Any other relevant information
- This takes time

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

Passive Surveillance - Challenges

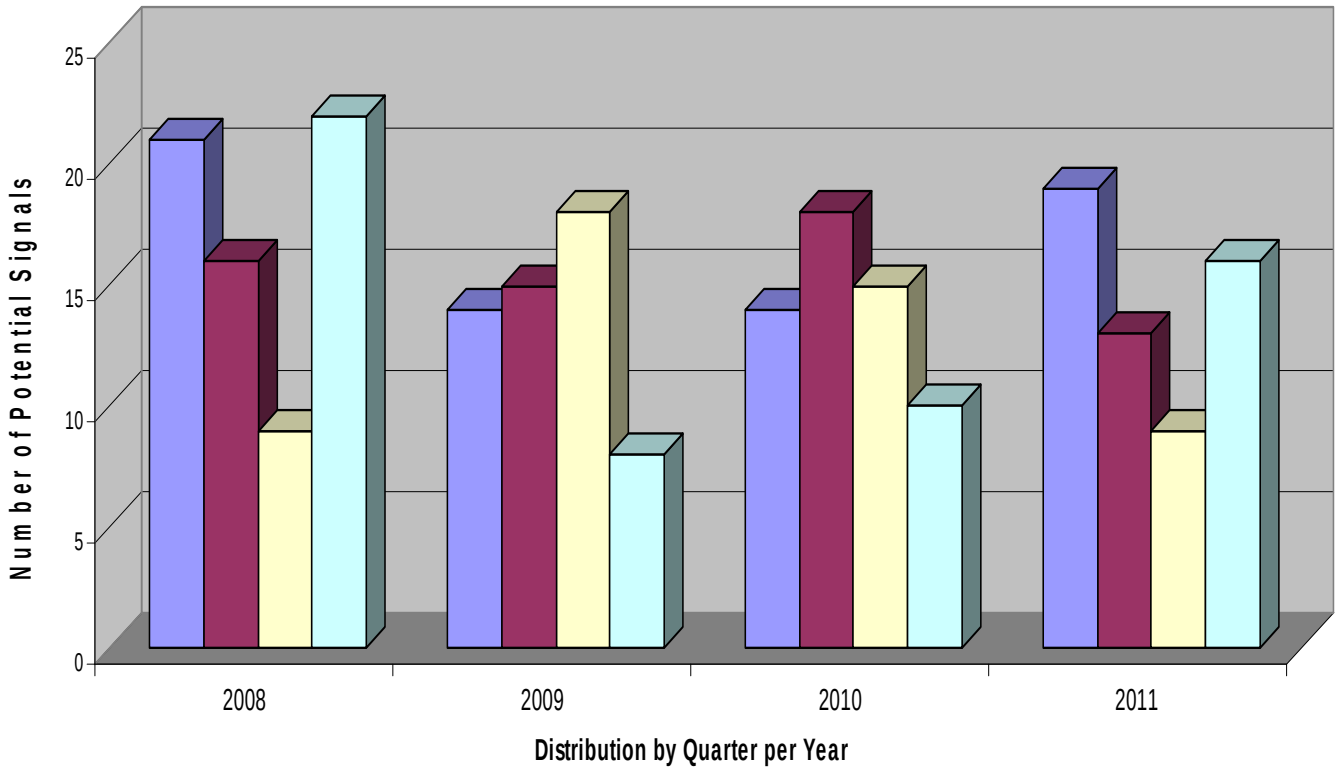
- Case reports, as a whole, often lack important clinical details
- Need to involve stakeholders
- Need refinement of signal detection methods, as numbers of reports increase
- Can this be automated?

The ASTER Experience

- ASTER
  - ADE Spontaneous Triggered Electronic Reporting System
  - Longitudinal Medical Record (LMR), and HER
  - LMR automatically triggers ASTER when the clinician discontinues a medication due to an “adverse reaction”
  - A MedWatch form is generated and populated with data from LMR
  - 26 clinicians submitted 217 reports to FDA
- FDA’s review
  - Demographic and other easily derived objective data were in the reports
  - Other important data were missing or conflicting
    - Description of the AE, dates to supports a temporal relationship of the drug to the AE, and relevant laboratory data
  - Most of the reported ADEs were known non-serious ADES
- Conclusion
  - Approach is feasible and needs to be refined to improve report quality

** Sources: Linder et al. PDS 2010;19:1211-1215; Brajovic et al. PDS 2012*

Potential Signals of Serious Risks / New Safety Information Identified from AERS
January 2008 - December 2011
237 Potential Product - Safety Issues Posted



Results From Quarterly Reports From January 2008 to December 2010

Table. Results From Quarterly Reports From January 2008 to December 2010

Result	Quarterly Reports, Year, No. (%) 2008	2009	2010	Total
Potential safety signals, No.	60	45	48	**153**
Label changes	30 (50)	28 (62)	16 (33)	**74** (48)[b]
Subgroups[a]				
Warnings and Precautions	16 (53)	19 (68)	11 (69)	**46** (62)
Adverse Reactions	11 (37)	5 (18)	7 (44)	**23** (31)
Drug Interactions	2 (7)	1 (4)	0	**3** (4)
Dosage and Administration	1 (3)	1 (4)	0	**2** (3)
Boxed Warning	6 (20)	2 (7)	1 (6)	**9** (12)
Contraindications	0	1 (4)	1 (6)	**2** (2)
Use in Specific Populations	0	0	1 (6)	**1** (1)
REMS	2 (7)	2 (7)	0	**4** (5)
Withdrawn from market	0	0	1 (6)	**1** (1)

Abbreviation: REMS, Risk Evaluation Mitigation Strategy.
[a] Calculated from the number of actual label changes.
[b] The calculated 48% total label changes includes the 1 drug withdrawn from the market and those drugs with newly implemented REMS.

Powers, A. et al. Arch Intern Med 2012;172:72-73.

ARCHIVES OF INTERNAL MEDICINE

Epidemiologic Studies and Clinical Trials of Drug Safety

Clinical Trial Data Are Important for Adverse Events That Have a High Background Prevalence

- Tegaserod
  - Myocardial infarction
- Sibutramine
  - Myocardial infarction
- Anti-depressants
  - Suicidal behavior
- Anti-epileptics
  - Suicidal behavior

Clinical Trials for Drug Safety - Challenges

- Proper endpoint selection
- Relevant patient population
  - May be different from population used for efficacy studies
- Choice of comparator
  - Active vs. placebo
  - Clinical relevance
- Adequate sample size
- Ethical issues
  - Institute of Medicine Report

Observational Studies Have Revealed Important Safety Findings

- Combined Hormonal Contraceptives
  - Arterial thrombosis
  - Deep venous thrombosis
- Phenylpropanolamine
  - Cerebral hemorrhage
- Pergolide
  - Valvulopathy

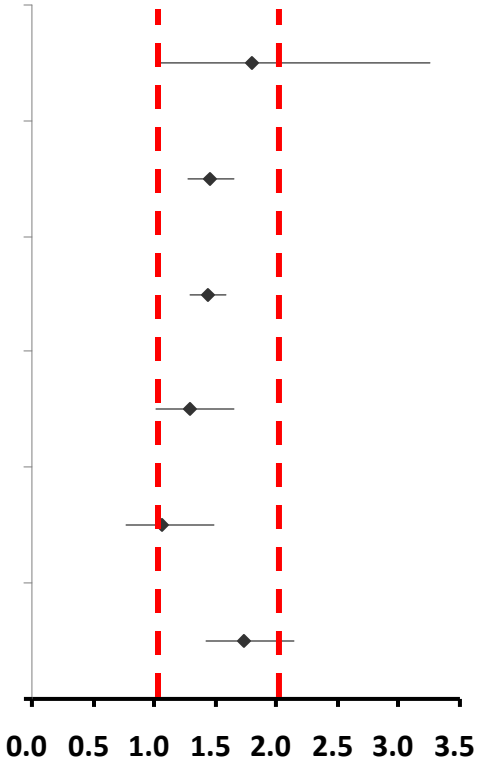
Using Large Databases

- Potential source of data for large observational studies
  - Case-control studies
  - Cohort studies
- Need to understand the output of such systems
- Not a replacement for careful clinical evaluation

Observational Studies - Challenges

- Need good data sources
  - Large data sources are not always the best sources
- Need robust methods to adjust for confounders
  - Residual confounding can still be a problem
- If the database is large enough, ANY finding can be statistically significant
  - Need careful interpretation

Effect Measures -- A Not-so-random Sample of Some Recent Drug Safety Issues



Rosiglitazone - MI – FDA RTC meta-analysis – OR

PPI - Hip Fracture – Case-Control Study #1 – OR

PPI - Hip Fracture – Case-Control Study #2 – OR

Oral Bisphosphonates - Esophageal Cancer – Nested Case-Control Study – RR

Oral Bisphosphonates - Esophageal Cancer – Cohort Study – HR

Drosperinone - VTE – Cohort Study – HR

Sources:

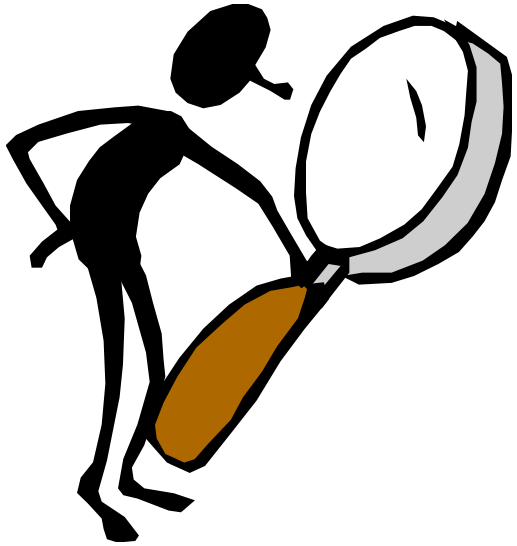
Rosiglitazone -http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf

PPI #1 – Vestergaard et al. Calcif Tissue Int. 2006;79:76-83. PPI #2 – Yang et al. JAMA 2006;296:2947-53 Oral bisphosphonates #1 – Cardwell et al JAMA 2010;304:657-63

Oral bisphosphonates #2 – Green et al. BMJ 2010;341 Drosperinone - http://www.fda.gov/Drugs/DrugSafety/ucm273021.htm

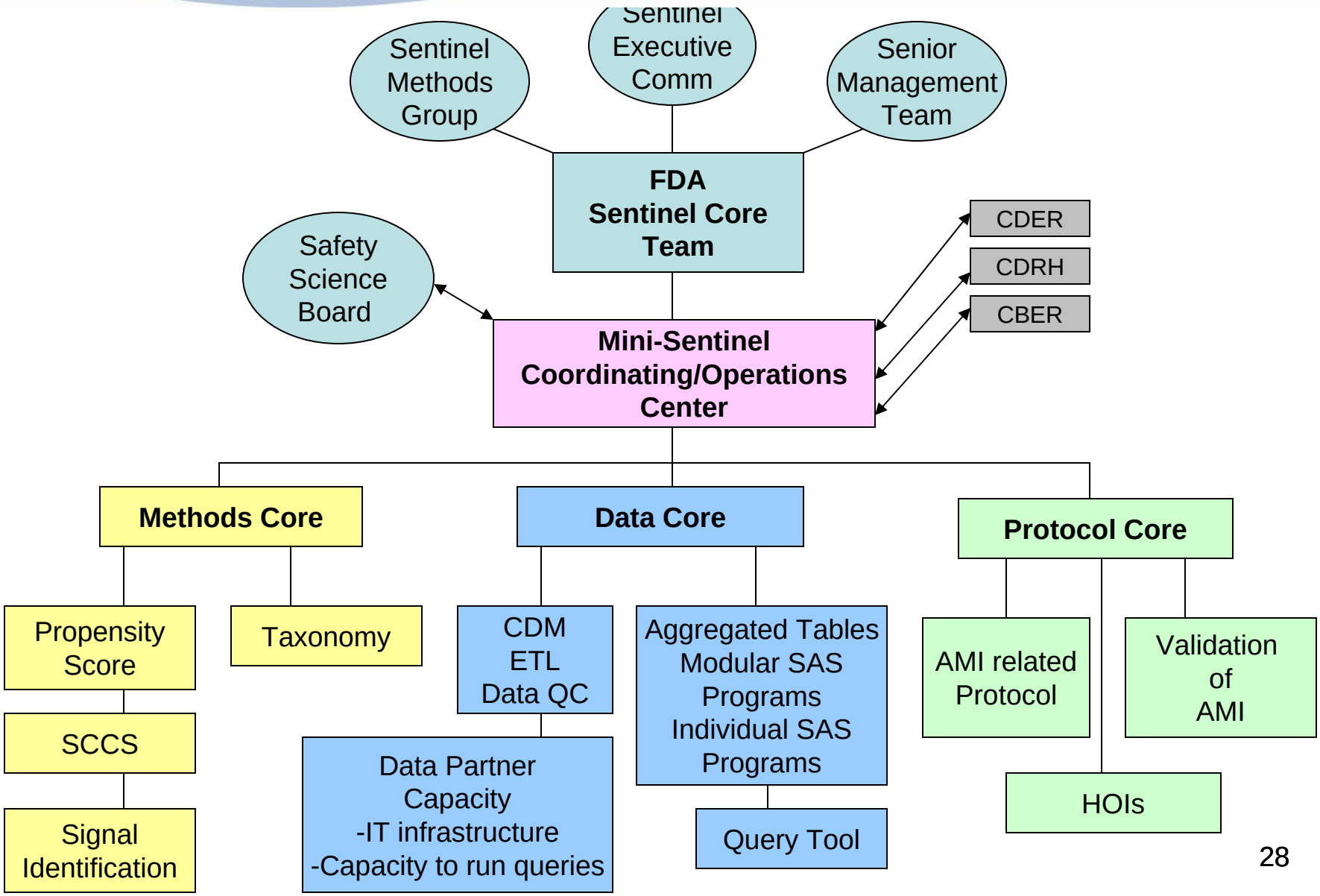
Active Surveillance

- Actively looking
- Can be:
  - Disease-based
  - Drug-based
  - Setting-based
- Can use large healthcare databases for surveillance



Sentinel Initiative

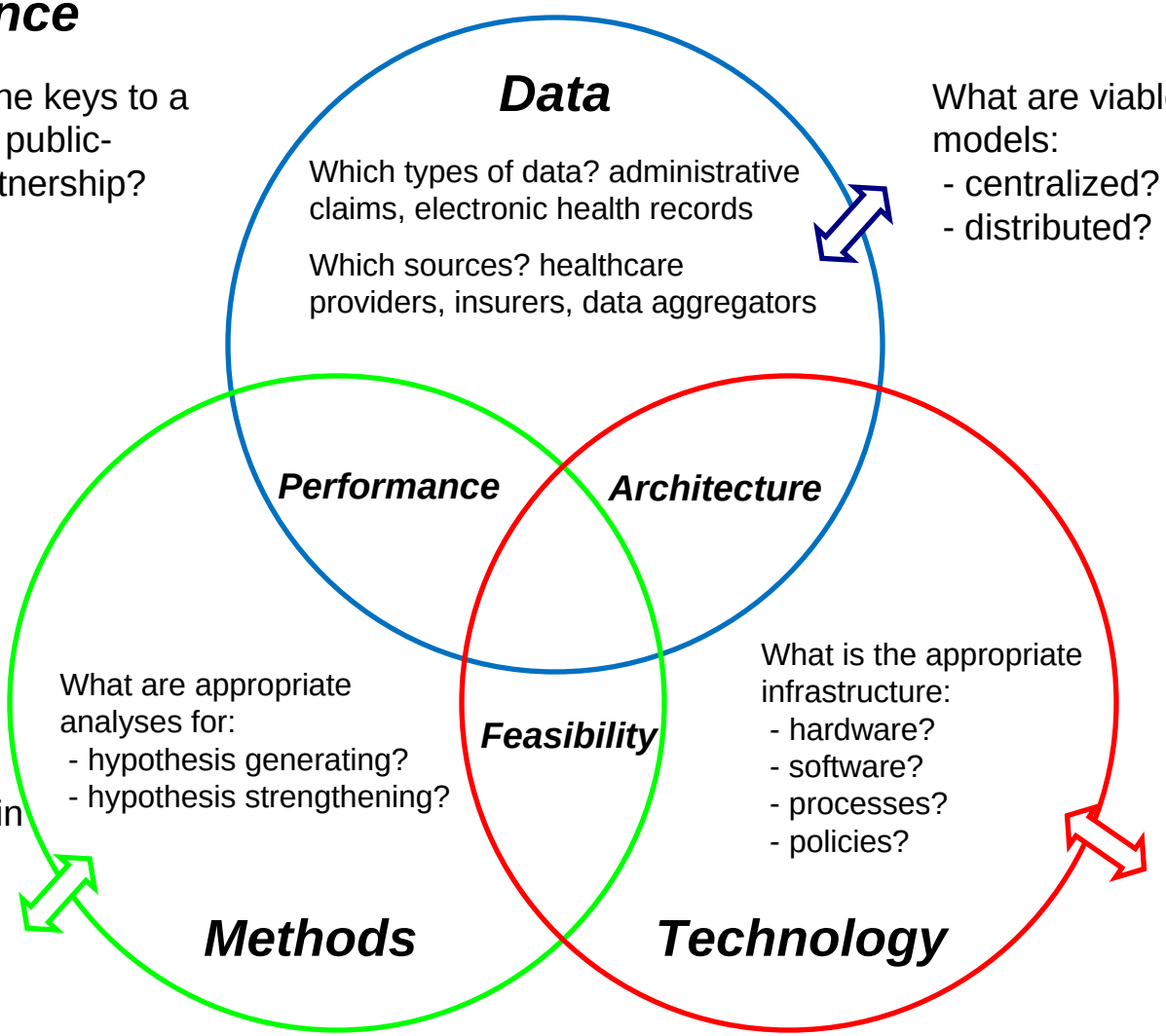
- FDA initiative
- Use large databases from multiple sources
- Cover a large number of lives
  - 25 million in 2010
  - 100 million in 2012
- Two components:
  - Mini-Sentinel
  - Federal Partners Collaboration


Sentinel Methods Group
Sentinel Executive Comm
Senior Management Team
FDA Sentinel Core Team
Safety Science Board
CDER
CDRH
CBER
Mini-Sentinel Coordinating/Operations Center
Methods Core
Data Core
Protocol Core
Propensity Score
SCCS
Signal Identification
Taxonomy
CDM
ETL
Data QC
Data Partner Capacity
-IT infrastructure
-Capacity to run queries
Aggregated Tables
Modular SAS Programs
Individual SAS Programs
Query Tool
AMI related Protocol
Validation of AMI
HOIs

Active Surveillance - Challenges

Governance

What are the keys to a successful public-private partnership?



What are viable data access models:
- centralized?
- distributed?

What are appropriate analyses for:
- hypothesis generating?
- hypothesis strengthening?

How to maintain collaborations and engage research community?

What is the appropriate infrastructure:
- hardware?
- software?
- processes?
- policies?

What are best practices for protecting data?

Risk Management

- FR Notice published on March 27, 2008 identified 16 drugs deemed to have REMS; http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-6201.pdf

- As of April 2, 2012 2011, 10 REMS have been approved for drugs deemed to have a REMS:

Tracleer	Isotretinoin
Letairis	Mifeprex
Thalomid	Actiq
Revlimid	Tikosyn
Lotronex	Tysabri

Medication Guides and REMS

- Medication Guides as Part of REMS
  - FDA may approve a MG under 21 CFR part 208 ***without*** requiring a REMS
    - When MG as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 208.1
  - May be few occasions when MG will be included in a REMS

- Medication Guides required as part of REMS are subject to the assessment and modification provisions under sections 505-1 (g) and (h) of the FD&C Act.
  - By eliminating the requirement for many Medication Guide only REMS, the number of patient surveys will decrease

- Previous policy was to approve all new Medication Guides , or existing Medication Guides with safety-related changes, as an element of a REMS

- Guidance for Industry reverses that policy
  - Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) (November, 2011)

Status of REMS Guidance Development

- Guidance on the Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications
  - Draft published 9/30/09; first comment period closed 12/30/09; comment period reopened for public meeting; closed 8/31/2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

Framework for standardizing REMS

- Articulate criteria for deciding whether a REMS is needed
- Articulate criteria for deciding what elements of a REMS are necessary
- Inform thinking through assessments of existing REMS with input from DSaRM AC and stakeholders
- Standardize REMS materials such as prescriber, pharmacist, and patient enrollment forms
- Provide prescriber education through existing continuing education mechanisms
- Use existing pharmacy systems to implement REMS that require pharmacy verification of various elements, such as prescriber education or patient testing.
- Integrate REMS into electronic health records and e-prescribing

Summary of Selected FDAAA Activities

Postings of Postmarketing Drug Safety Evaluations

- Based on data 18 months post-approval, (approved since September 27, 2007) or after 10,000 patients have taken the drug, whichever is later (FDAAA Sec. 915)

- 75 CDER drug evaluations posted (through June 2011):
  - 22 NMEs
  - 53 Non-NMEs

- NMEs:
  - No new safety issues requiring a labeling change or other actions were discovered.

- Non-NMEs:
  - Four labeling changes have been recommended for adverse events
  - Ten additional products had issues that require other actions or further monitoring.

FDAAA SLC and PMR Numbers
March 25, 2008 – March 1, 2012

Postmarketing Requirements (PMRs)

- Over 496 PMRs have been required for both NDAs and BLAs

Safety Labeling Changes (SLC)

- 65 SLC invoked
- Mostly for drug classes
- SLC orders issued 9 times - ESAs, Zyprexa, Symbyax, Geodon, propylthiouracil, Vasotec, Advair Diskus/HFA and Serevent Diskus, Symbicort; antipsychotics (ANDAs only)

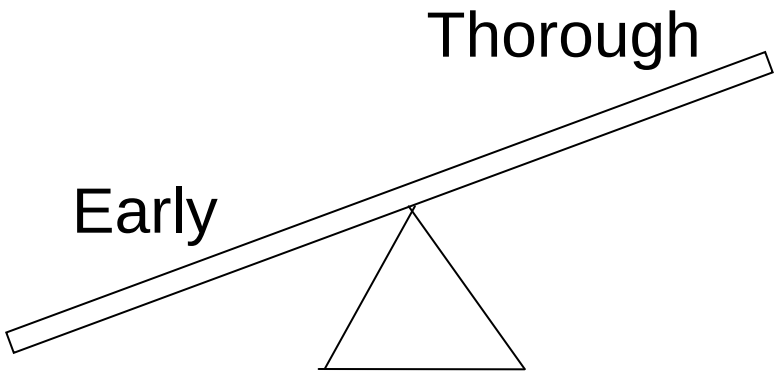
REMS Summary:
March 25, 2008 – March 1, 2012

- New REMS approved for approximately 200 products
  - 125 with Medication Guide only REMS (105 have since been released)
  - 36 drug products with REMS have elements to assure safe use (ETASU) (includes Deemed REMS)
    - 1 ETASU REMS released
    - 2 REMS had ETASU released, but have communication plan
    - 2 single shared system REMS
      - TIRF- includes 6 drug products
      - Isotretinoin iPLEDGE program
    - 10 of the 16 Deemed REMS are approved; only 4 of the remaining 6 are currently marketed
  - 40 had a communication plan as the primary element and most also had a Medication Guide
    - 7 have since been released
- Currently, there are 86 approved REMS

Risk Communication

Communications Principles

- Important drug safety information
- Emerging drug safety information
- Early notification versus thorough review
  - A natural tension
  - FDA leans toward early
- The challenge of getting messages across



Safe Use – The Case of Cisapride

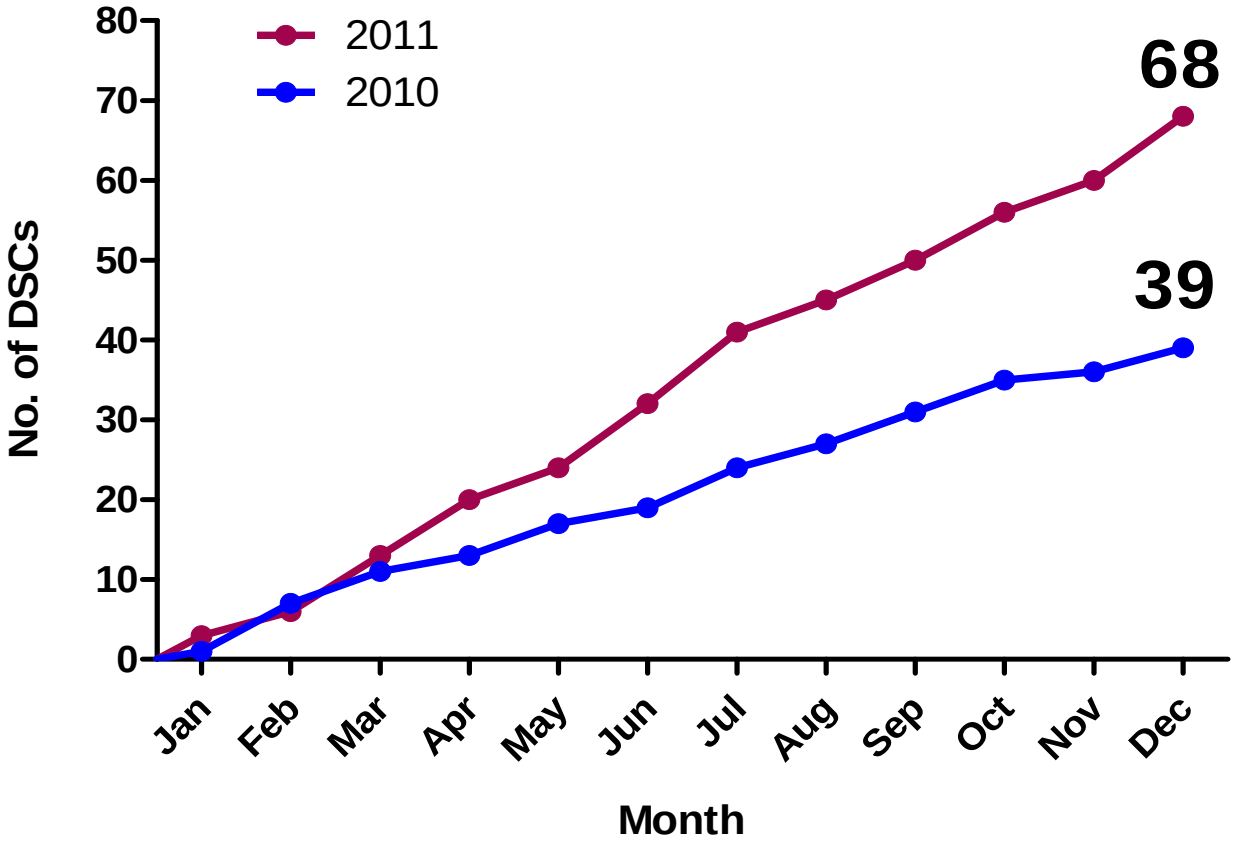
- Cisapride – gastrointestinal promotility agent
- Can cause life-threatening cardiac arrhythmias if
  - Used with certain contraindicated concomitant medications
  - Used in person with certain other diseases
- Regulatory Action – June 1998:
  - Boxed warning contraindicating use in certain patients and with certain concomitant medications
  - Company sent Dear Healthcare Provide Letter to practitioners
- Study: Look at prescribing patterns one year before and one year after regulatory action
- Finding:
  - High prevalence of contraindicated use at three sites
  - No change in prescribing patterns after regulatory action

Proportion of New Cisapride Users With Contraindicated Use Before and After Regulatory Action

Adapted from Smalley et al. Contraindicated Use of Cisapride. JAMA 2000;284:3036-3039

Drug Safety Communications

Cumulative Number of Drug Safety Communications



Looking to the Future

Building Safety Into Drug Development

- Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation
  - Quantitiative data analysis
  - Individual case analysis
  - Analysis of signals
- Guidance for Industry: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
  - Thorough QT/QTc studies
  - Interpretation of ECG data in clinical trials
- Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
  - Appropriate design of Phase 2/3 trials to assess cardiovascular risk
  - Methods for meta-analysis
  - Criteria for pre-approval and post-approval testing

Weighing the Evidence

- Weighting all the data
  - Pharmacovigilance data may be only one piece of data
- Weighing the benefits and the risk
- Arriving at a conclusion

Building Capacity

- As drug safety science becomes more important and more complex
  - Need to build more capacity
  - Need to increase collaborations
  - Need to share best practices
- A global endeavor

Thank you