Approaches to Marketed Medical Product Safety Assessment: An FDA Perspective

Judith A. Racoosin, MD, MPH
Sentinel Initiative Scientific Lead, FDA

Covering for
Ann W. McMahon, MD, MS
Deputy Director, Division of Pharmacovigilance I
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

February 22, 2010

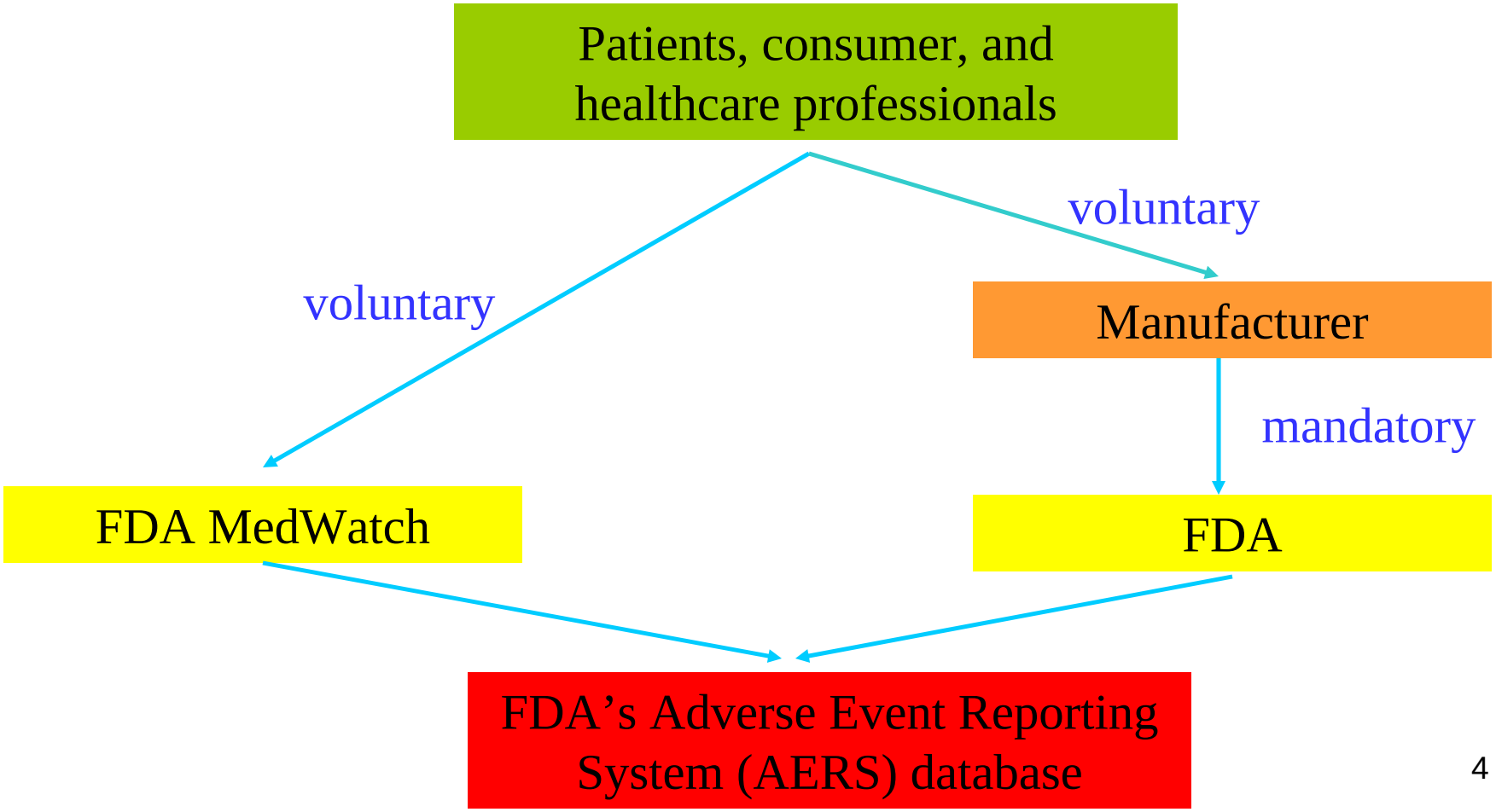
OUTLINE

- Passive surveillance systems
- Initiatives to use large databases for active surveillance
- New Molecular Entity Pilot Project
- Outline of the 2007 Food and Drug Administration Amendments Act (FDAAA)

Adverse Event Reporting System (AERS)

- Computerized database
- Contains human drug and “therapeutic” biologic reports
- > 4 million reports
- exception = vaccines (VAERS)

How Safety Reports Get to FDA



Initial Screening of Reports

- Daily “in-box” review of reports
  - all serious unlabeled;
  - all direct;
  - some periodic
  - Expedited “enhanced pharmacovigilance” reports
- Main mission: To identify and assess previously unrecognized (unlabeled), serious AEs

Case Evaluation

- Temporal relationship
- Dechallenge/rechallenge
- Comorbidities
- Concomitant medications
- Absence of symptoms prior to exposure

Case Evaluation (2)

- Consistent with pharmacological effects
- Consistent with known effects in the class
- Support from pre-clinical studies or clinical trials
- Alternative explanations
- Other medical or laboratory findings

Case Evaluation (3)

- Determine if report is well documented and worth pursuing
- Follow-up with reporter
- Identify clinically relevant cases in AERS
- Generate AERS standard report

Good Case Report*

- Description of event
- Suspected and concomitant products therapy details
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family Hx, other risk factors
- Documentation of the diagnosis
- Dechallenge and rechallenge

*http://www.fda.gov/cder/guidance/6359OCC.htm

Challenges in Evaluating Case Reports

- Cases often confounded by other possible etiologies
- Absence of complete diagnostic information

Examples of Safety Signals

- New unlabeled adverse events
- An observed increase in a labeled event in its severity or specificity
- Newly identified at-risk population

Primary Areas of Utility of Spontaneous Reports

- Signal detection

- Adverse event characterization

AERS Limitations

- Duplicate reporting
- Extensive underreporting
- Quality of report is variable
- Reporting biases
- Actual numerator (# of events in pop) & denominator (# of exposed patients in pop) not known

AERS Strengths

- Includes all U.S. marketed products
- Simple, inexpensive reporting system
- Detection of events not seen in clinical trials ("signal generation")
- Especially good for events with rare background rate
- Case series evaluation: identification of trends, drug indication, population, and other clinically significant emerging safety concerns

AERS Strengths (2)

- Large Patient Population including:
  - Elderly, children, women, ethnic groups, pregnancy, co-morbidities
- Wider indications than those studied
- Chronic use
- Complicated patients, complicated AERS cases

OUTLINE

- Passive surveillance systems
- Initiatives to use large databases for active surveillance
- New Molecular Entity Pilot Project
- Outline of the 2007 Food and Drug Administration Amendments Act (FDAAA)

Sentinel Initiative Overview

- Develop an active electronic safety monitoring system to:
  - Strengthen FDA's ability to monitor postmarket performance of medical products
  - Augment, not replace, existing safety monitoring systems
  - Enable FDA to access existing automated healthcare data by partnering with data holders (e.g. insurance companies with large claims databases, owners of electronic health records, others)

How may Sentinel complement what we are already doing?

- Safety issues may be identified and evaluated in near real-time
- Sentinel expands the capacity for evaluating safety issues
  - Improved access to subgroups, special populations
  - Improved precision of risk estimates due to expanded number of populations available for study
- Active surveillance may identify an increased risk of common AEs (e.g., MI, fracture) that health care providers may not suspect are related to medical products

A Work in Progress

May ’08: Sentinel Initiative launched with release of initial report

- A long-term project; will be implemented in stages and will necessarily evolve
- In first year, 8 small contracts awarded to inform data infrastructure needs, scientific operations, governance, privacy, and stakeholder outreach

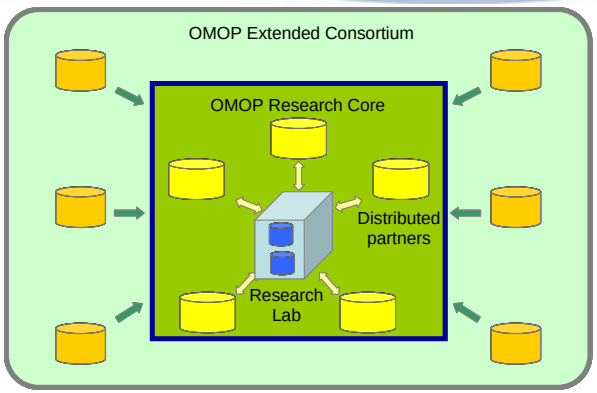
Communication

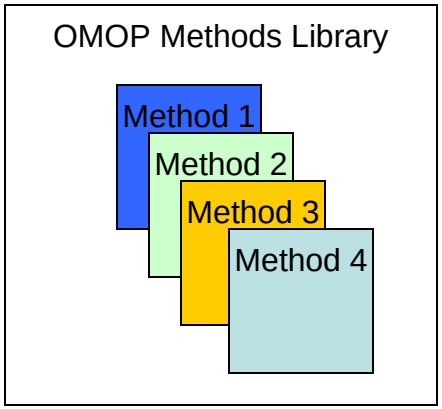
- Efforts to provide information on status of initiative and obtain input from stakeholders
  - Website
    http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm
  - Public outreach
  - Internal meetings

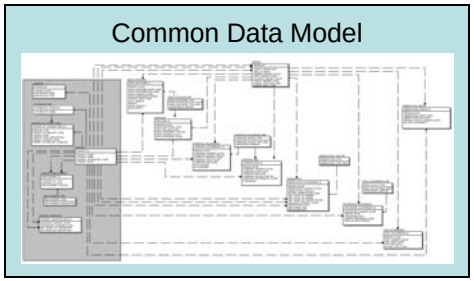
Observational Medical Outcomes Partnership
http://omop.fnih.gov

- Public-Private Partnership with FNIH, FDA, and PhRMA
- Conducts experiments to assess value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs
- Tests approaches for creating the infrastructure for accessing and managing required data
- Enables the evaluation of a possible governance model, consisting of an Executive Board, and Scientific and Technical Advisory Boards

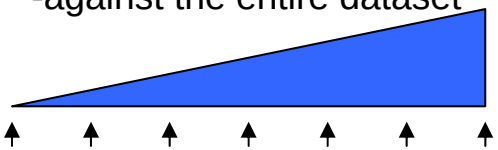
OMOP Experiment Research Workflow







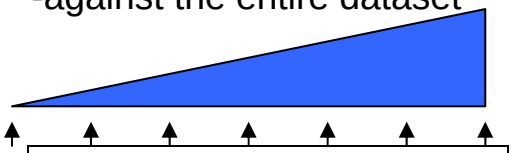
Testing in each source:
-accumulating over time
-against the entire dataset



Health Outcomes of Interest
Angioedema
Aplastic Anemia
Acute Liver Injury
Bleeding
GI Ulcer Hospitalization
Hip Fracture
Hospitalization
Myocardial Infarction
Mortality after MI
Renal Failure

Drugs
ACE Inhibitors
Amphotericin B
Antibiotics
Antiepileptics
Benzodiazapines
Beta blockers
Bisphosphonates
Tricyclic antidepressants
Typical antipsychotics
Warfarin

Testing in each source:
-accumulating over time
-against the entire dataset



Non-specified conditions

-All outcomes in condition terminology

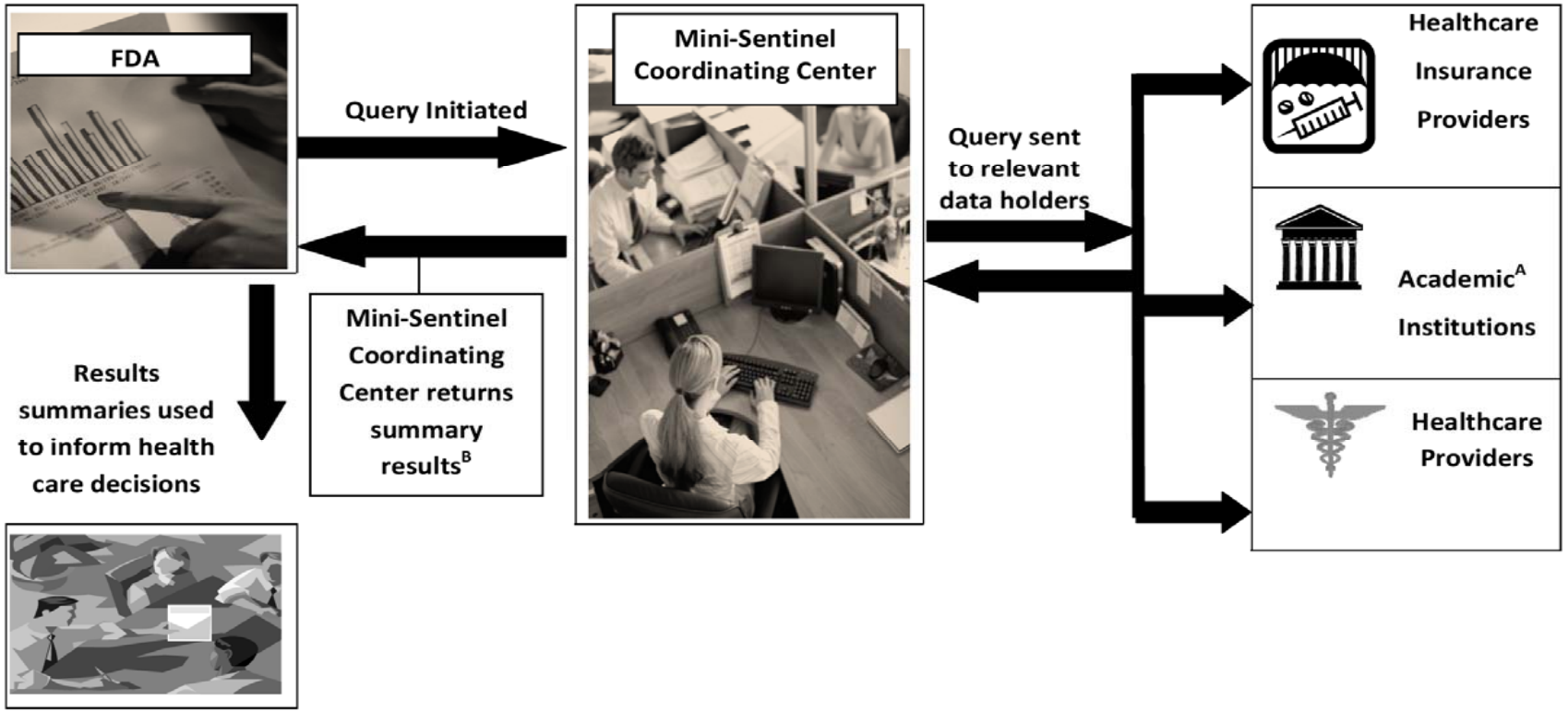
-'Labeled events' as reference
-Warning
-Precautions
-Adverse Reactions
-Postmarketing Experience

Mini Sentinel

Harvard Pilgrim Healthcare

- Develop a coordinating center for a distributed system
  - Access three or more health data environments with varied attributes to conduct analyses
  - Convene a Planning Board to develop governing documents and establish a Safety Science Committee charged with the day-to-day operations
  - Develop a means for secure communication with contracted data holders
- Evaluate emerging methods in safety science
  - Develop epidemiological and statistical methodologies for signal detection, signal strengthening, and signal validation
  - Test such methodologies in the evaluation of FDA-identified medical product-adverse event pairs of concern

Overview of the Mini-Sentinel Query Process



A. Only those academic institutions with automated data will be recipients of queries.

B. No entities will have access to protected health information that they do not already hold. Instead, those whose queries are accepted by the **Mini-Sentinel Coordinating Center** for processing will receive results summaries from analyses conducted by each data holder that receives and agrees to respond to those queries. Results summaries will not include protected health information.

Federal Partners Collaboration

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- Identify medical product – AE pairs to evaluate
- Evolve active surveillance methodologies
- Evaluate interpretability of query findings resulting from a decentralized analytic approach

OUTLINE

- Passive surveillance systems
- Initiatives to use large databases for active surveillance
- New Molecular Entity Pilot Project
- Outline of the 2007 Food and Drug Administration Amendments Act (FDAAA)

New Molecular Entity (NME) Postmarketing Safety Evaluation Pilot Program*

- Pilot Project Fall, 2006-March, 2008
- Collaboration of 2 Offices within Center for Drugs:
  - Office of Surveillance and Epidemiology
  - Office of Drug Evaluation I
- Data routinely reviewed
  - Reports of serious and unexpected adverse drug experiences
  - Periodic safety reports
  - Medical literature
  - Data from clinical trials
  - Data from other drugs within the same pharmacologic class
- Purpose: Determine the value of an additional effort: the periodic, systematic, and collaborative evaluation of the safety of 5 marketed drugs
- Final Report posted on website:

*http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm185252.htm

NME Pilot Product Details and Resources Used to Complete Pilot Evaluations

NME	Number of Months After Approval	Number of Patients Receiving Prescription	Crude Number of AERS Reports	Number of Hours Spent on NME Evaluation	Number of Safety Issues Identified for Follow-up
Cymbalta® (duloxetine)	31	3,059,937	6,490	215	8
Ranexa® (ranolazine)	17	39,074	94	161	0
Apokyn® (apomorphine)	41	2,764	245	111	3
Abilify® (aripiprazole)	64	2,156,400	6,183	369	6
Azilect® (rasagiline)	22	32,732	49	182	5

Conclusions: NME Pilot Project

1. The process required extensive collaboration between CDER Offices.
2. Pilot project succeeded in identifying some new, previously unknown safety issues.
3. These evaluations required considerable resources from more than one Office, including hands on evaluation of individual cases, despite automation of some of relevant data.

OUTLINE

- Passive surveillance systems
- Initiatives to use large databases for active surveillance
- New Molecular Entity Pilot Project
- Outline of the 2007 Food and Drug Administration Amendments Act (FDAAA)

Overview of FDAAA

Title I – Prescription Drug User Fee Act (PDUFA)

Title II – Medical Device User Fee Act

Title III – Pediatric Medical Device Safety & Improvement Act

Title IV – Pediatric Research Equity Act (PREA)

Title V – Best Pharmaceuticals for Children Act (BPCA)

Title VI – Reagan-Udall Foundation

Title VII – Conflicts of Interest

Title VIII – Clinical Trials Database

Title IX –Enhanced Authorities Regarding Postmarketing Safety of Drugs

Title X – Food Safety

Title XI – Other Provisions

Title IX –Enhanced Authorities Regarding Postmarketing Safety of Drugs

- The statute contains important new authorities to require
  - Postmarket studies and clinical trials
  - Safety labeling changes
  - Risk Evaluation and Mitigation Strategies (REMS)
    - to ensure that the benefits of a drug outweigh its risks
- The new safety authorities in Title IX, Subtitle A of FDAAA took effect on March 25, 2008.
- Summary of FDA Implementation of FDAAA

http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/UCM184275.pdf

Excerpts from summary of FDAAA Implementation (re: Title IX)

- Between March 25, 2008 and September 14, 2009
  - FDA (CDER and CBER) issued 74 letters with postmarketing requirements to assess safety issues for drugs and biologics.
  - FDA (CDER and CBER) used its new authorities to require safety label changes 22 times. Most of the required safety label changes were invoked for classes of drugs or biologics.
  - Among 275 applications and efficacy supplements approved by CDER and CBER, CDER approved 78 REMS,
    - 59 REMS include only a Medication Guide
    - 19 REMS include elements other than a Medication Guide (e.g., a communication plan and/or elements to assure safe use, and also, in some cases, a Medication Guide too).
      - 6 have elements to assure safe use

CONCLUSIONS

- FDA is incorporating information from a pilot program using a new systematic method to review the safety profiles of new molecular entities (NMEs) on a regularly scheduled basis after approval.
- FDA will continue to engage the public and private sectors in a discussion of opportunities for public and private sector collaboration on activities such as data collection and risk identification in the area of post-marketing safety.
- An exciting new challenge for FDA is the implementation of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

CONTRIBUTORS

- Ann McMahon
- Min Chu Chen
- Cindy Kortepeter
- Judy Racoosin
- Gerald Dal Pan