

# FDA's Mini-Sentinel Program to Evaluate the Safety of Marketed Medical Products

# **Progress and Direction**

Richard Platt Harvard Pilgrim Health Care Institute Harvard Medical School for the Mini-Sentinel Investigators

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# **Mini-Sentinel**

- Develop scientific operations for active medical product safety surveillance
- Create a coordinating center with continuous access to automated healthcare data systems, and the following capabilities:
  - Develop and evaluate scientific methods that might later be used in a fully-operational Sentinel System.
  - Offer FDA the opportunity to evaluate safety issues in existing automated healthcare data system(s) and learn more about barriers and challenges.



#### The annotated Mini-Sentinel

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**: 1–8 Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2343

ORIGINAL REPORT

The U.S. Food and Drug Administration's Mini-Sentinel program:

- Supplement to Pharmacoepidemiology and Drug Safety
- 34 peer reviewed articles; 297 pages
- Goals, organization, privacy policy, data systems, systematic reviews, stats/epi methods, record retrieval and review, protocols for drug/vaccine studies...
- Open access!
- http://onlinelibrary.wiley.com/doi/10.1002/pds.v21.S1/issuetoc



#### 🔇 www.mini-sentinel.org RSS 🔜 | Font Size 🔜 🙀 | 🚺 SHARE **Mini-Sentine** Search Mini-Sentinel is a pilot project spreased by the <u>to.S. Food and Drug</u> Administration (FDA) to inform and facilitate development of a fully operation active surveillance (SERIE), the Sentinel System, for monitor TDA- regulation of a noducts. About Us Assessments Data Publications **Related Links** Home NEW POSTINGS Drugs that act on RAAS and angioedema Smoking cessation drugs & tate development of a fully operational cardiovascular outcomes ntinel System, for monitoring the safety of Angiotensin II receptor blockers & celiac disease Anti-diabetes drugs & acute myocardial one piece of the Sentinel Initiative, a multi-faceted effort by the infarction velop a national electronic system that will complement existing Mini-Sentinel Common Data Model v2.0 methods of safety surveillance. MSDD At-a-Glance - December 12, 2011 Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.



#### Stages of postmarket surveillance

	Signal Generation	Signal Refinement	Signal Evaluation
Aim = Identify excess risk	All (suspected and unanticipated) adverse events (AEs), all products	Specific AE:product pairs of concern	A highly suspected AE:product pair
Approach		Repeated assessment of accumulating experience or one-time expedited assessment	
Example		Active surveillance in Mini-Sentinel and VSD using coded electronic health information	



#### Mini-Sentinel goals

- Develop a <u>consortium</u>
- Develop <u>policies and procedures</u>
- Create a <u>distributed data network</u>
- Evaluate/develop <u>methods</u> in safety science
- □ <u>Assess</u> FDA-identified topics



#### Active surveillance activities

- Characterize populations, treatments, and health events
- For older products, assess concerns arising from any source
- □ Assess impact of FDA actions
- For new products, monitor accumulating experience for pre-specified potential adverse outcomes



### Mini-Sentinel goals

#### Develop a <u>consortium</u> of data partners and other content experts



# **Mini-Sentinel Partner Organizations**



info@mini-sentinel.org



#### Leadership

Planning board – principal investigators, FDA, public representative

- Operations center
- Cores: data, methods, protocols
- Policy committee
- □ Safety science committee
- Privacy board
- Workgroups



### Mini-Sentinel goals

Develop a consortium

#### Develop <u>policies and procedures</u>



### Governance principles/policies

- Public health practice, not research
- Minimize transfer of protected health information and proprietary data
- Public availability of "work product"
  - Tools, methods, protocols, computer programs
  - Findings
- Data partners participate voluntarily
- Maximize transparency
- Confidentiality
- Conflict of Interest



### Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a <u>distributed data network</u> with access to electronic health data and full text records
  - Develop secure communications capability



#### Activities

Data capacity	Distributed methods	Signal alerting
<ul> <li>Integrity</li> <li>Common data model</li> <li>Data completeness</li> <li>Data validity</li> <li>Health Outcome of Interest detection and validation</li> <li>Environments</li> <li>Claims</li> <li>EHRs</li> </ul>	<ul> <li>Distribution and retrieval</li> </ul>	

#### Applications



# Mini-Sentinel's Evolving Common Data Model

Administrative data

- Enrollment
- Demographics
- Outpatient pharmacy dispensing
- Utilization (encounters, diagnoses, procedures)
- EHR data
  - Height, weight, blood pressure, temperature
  - Laboratory test results (selected tests)
- Registries
  - Immunization
  - Mortality (death and cause of death)



#### The Mini-Sentinel Distributed Database

- Populations with well-defined person-time for which medically-attended events are known
- 126 million individuals\*
  - 345 million person-years of observation time (2000-2011)
  - 44 million individuals currently enrolled, accumulating new data
  - 27 million individuals have over 3 years of data

\*As of 12 December 2011. The potential for double-counting exists if individuals moved between data partner health plans.



#### The Mini-Sentinel Distributed Database

□ 3 billion dispensings

- Accumulating 37 million dispensings per month
- 2.4 billion unique encounters
  - 40 million acute inpatient stays
  - Accumulating 41 million encounters per month including over 400,000 hospitalizations

 $\Box$  13 million people with  $\geq$ 1 laboratory test result



#### Why a Distributed Database?

- Avoids many concerns about inappropriate use of confidential personal data
- Data Partners maintain physical control of their data
- Data Partners understand their data best
  - Valid use / interpretation requires their input
- Eliminates the need to create, secure, maintain, and manage access to a complex, central data warehouse



# **Mini-Sentinel Distributed Analysis**





#### **Mini-Sentinel Query Tool**

- □ Enhanced version of PopMedNet<sup>™</sup> software application
- Queries summary counts of each table in the local implementation of the common data model.
  - Summary tables reside with the Data Partners
  - Software securely transmits queries
- Data Partners can choose to evaluate queries before execution or queries can be run automatically.



#### Mini-Sentinel Modular Programs

- 1. Drug exposure for a specific period
  - Incident and prevalent use combined
- 2. Drug exposure with a specific condition
  - Incident and prevalent use combined
  - Condition can precede and/or follow
- 3. Outcomes following first drug exposure
  - May restrict to people with pre-existing diagnoses
  - Outcomes defined by diagnoses and/or procedures
- 4. Concomitant exposure to multiple drugs
  - Incident and prevalent use combined
  - May restrict to people with pre-existing conditions



#### Detecting and Validating Health Outcomes

Detecting potential cases using administrative data

- 20 systematic reviews: algorithms to detect health outcomes of interest
- Validating cases using full text records
  - Acute myocardial infarction
    - 93% of charts retrieved (143/153)
    - 86% of cases confirmed by expert panel



# Blood Safety Continuous Active-Surveillance Network (Blood-SCAN)

- □ Strengthen FDA's hemovigilance capabilities
  - Initial focus on recipient safety
  - Emphasis on non-infectious complications



http://www.newsrx.com/images/sized/ uploads/topics/blood1-300x300.jpg

- Create and characterize a Blood-SCAN distributed database
  - Develop an active surveillance system for regulated blood and blood-derived product use
  - Harmonize Blood-SCAN with existing US biovigilance efforts



#### **Blood-SCAN Proposed Activities**

Assess current ability to evaluate blood product exposures and outcomes

Identify additional data in Mini-Sentinel EHRs

Identify other linkable sources of blood product exposure Characterize enhanced database ability to capture key exposures and outcomes Assess risk of thromboembolism after immunoglobulin



# Data development in progress

- Expand base population
- Incorporate data from immunization registries
- Develop capacity to assess blood products
- Completion of data checking of vital signs and laboratory data
- Outcome detection: 18 systematic reviews focused on outcomes of special interest for vaccine safety
- Outcome validation: Acute liver injury, acute renal failure, anaphylaxis, intussusception, venous thromboembolism



#### Data development: On the Horizon

- Additional data
  - Electronic Health Records
  - State birth registries
- Enhance/expand library of modular programs and summary tables
  - More kinds of pre-compiled data
  - More flexible exposure and outcome options
  - Automated confounder adjustment
  - Self-control designs



### Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network
- **C** Evaluate extant <u>methods</u> in safety science
  - Develop new epidemiological and statistical methods as needed



#### Activities

Data capacity	Distributed methods	Signal alerting
<ul> <li>Integrity</li> <li>Common data model</li> <li>Data completeness</li> <li>Data validity</li> <li>HOI validation</li> <li>Environments</li> <li>Claims</li> <li>Claims</li> <li>EHRs <ul> <li>Ambulatory</li> <li>Inpatient</li> </ul> </li> <li>Registries</li> <li>Other (blood banks, genetic data, etc.)</li> </ul>	<ul> <li>Distribution and retrieval</li> </ul>	<ul> <li>Design &amp; validity <ul> <li>Study design choice</li> <li>Automated confounding adjustment</li> </ul> </li> <li>Performance of <ul> <li>Sequential testing</li> <li>Data mining</li> </ul> </li> </ul>

#### Applications



#### Design and validity

#### **Taxonomy**:

- Expedited choice of design and analytic monitoring approach
- Identified generic attributes of exposure, outcomes, and relationships developed a decision table (Gagne et al, PDS supplement)
- □ Self-controlled designs:
  - **Developed guidance on** (Maclure, PDS supplement)
    - Strength/limitations, practicability in a monitoring setting
  - Tested a multivariate approach



### **Decision Table:**

#### 64 drug-outcome pair scenarios are linked to two basic designs strategies

Structured decision table to facilitate methods selection for particular active medical product monitoring scenarios									
Monitoring scenario characteristics with implication for design Characteristics of the (potential) exposure-HOI link			choice <sup>a</sup>	-	Monitoring scenario characteristics with implication for analytic choice <sup>a</sup>				
		Duration	Strength of						
	Onset of	of	confo	inding					
	exposure	exposure	Within-	Between-			Background	Background	
Exposure	risk	risk	person	person	HOI	Design sheiseb	irequency of	Irequency of	
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		10118/		addin cobodiy		1		Infrequent	1
Transient (e.g. vaccine, <i>initiation</i> of a drug; including episodic drug use [e.g. Immediate triptans] to the extent that the question pertains to its transient nature)				Negligible	Abrupt	self-controlled (or	Infrequent	Rare	2
						cohort) Rare	Dava	Infrequent	3
							Kare	Rare	4
			regingione	Insidious	<sup>2</sup> cohort (or self- controlled)	Infrequent	Infrequent	5	
						milequent	Rare	6	
						Rare	Infrequent	7	
			Negligible				Ture	Rare	8
	Short			Abrupt	self-controlled (or cohort)	Infrequent	Infrequent	9	
							Kare	10	
						Rare	Intrequent	12	
				Needs to be	Insidious	4		Infroquent	13
				addressed		self-controlled or cohort	Infrequent	Rare	14
								Infrequent	15
							Rare	Rare	16
			Needs to be addressed	Negligible	Abrupt	5	Infrequent	Infrequent	17



#### **Design and Validity**

#### Automated covariate adjustment

- A comprehensive approach to automated covariate adjustment is being developed for Propensity Score and Disease Risk Score methods (Rassen & Schneeweiss, PDS supplement)
- Simulation studies indicate theoretical biases (M-Bias and z-Bias) are not usually a problem (Myers et al. AJE 2011;174:1213)



### Performance of signal alerting algorithms

#### Sequential testing

- Reviewed methods 'state-of-the-art'
- Developed guidance on sequential designs customized for observational safety settings (Nelson et al, PDS supplement)
- Simulation to compare performance (Cook et al, PDS supplement)
  - Type 1 error rate, power, time-to-signal detection
  - Varying outcome prevalence, exposure & confounder complexity



#### Methods development: In progress / Future directions

- Sequential monitoring using inverse probability weighting
- Semi-automated or automated confounding control using propensity and disease risk scores
- Simulation framework for evaluating alerting algorithms
- Anonymous linkage across data sources
- Analytic approaches in a distributed data setting



### Mini-Sentinel goals

- Develop a consortium
- Develop policies and procedures
- Create a distributed data network
- Evaluate/develop methods in safety science

#### **Evaluate** FDA-identified topics



#### Activities

Data capacity	Distributed methods	Signal alerting	
<ul> <li>Integrity</li> <li>Common data model</li> <li>Data completeness</li> <li>Data validity</li> <li>HOI validation</li> <li>Environments</li> <li>Claims</li> <li>Claims <ul> <li>EHRs</li> <li>Ambulatory</li> <li>Inpatient</li> </ul> </li> <li>Registries</li> <li>Other (blood banks, genetic data, etc.)</li> </ul>	<ul> <li>Distribution and retrieval</li> <li>Anonymous linkage across sources</li> <li>Analytic approaches in a distributed data setting</li> </ul>	<ul> <li>Design &amp; validity</li> <li>Expedited design choice</li> <li>Automated confounding adjustment</li> <li>Performance of</li> <li>Sequential testing</li> <li>Non test-based</li> <li>Decision analytic approaches</li> </ul>	

#### Applications

- Characterize exposures and health events, monitor accumulating experience
- Assess impact of FDA regulatory action



#### Active surveillance activities

#### Characterize exposures and health events



#### Rapid Queries of Exposures – Examples

- Drugs
  - Analeptics, Analgesics, Antihypertensives, Antiarrhythmics, Antiretrovirals, Antidepressants, Antipsychotics, Antibiotics, Bronchodilators, Cancer chemotherapy agents, Growth factor inhibitors, Intravenous iron, Smoking cessation drugs, Steroids
- Vaccines
  - Measles/mumps/rubella, rotavirus, human papilloma virus
- Devices
  - Hip replacement, Negative pressure wound therapy devices



#### Rapid Queries of Health Events – Examples

- Cardiovascular: Acute myocardial infarction, Hyperlipidemia
- Neurologic: Parkinson's disease,
   Progressive multi-focal leukoencephalopathy
- Gastrointestinal: Celiac disease, Ulcerative colitis, Crohn's disease
- Allergic: Severe cutaneous conditions, Anaphylaxis, Angioedema, Milk allergy
- Other: Osteonecrosis of the jaw



#### Prasugrel and Prior Stroke/TIA

- Prasugrel indicated to prevent thrombotic cardiovascular events in selected patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention.
- It is contraindicated in patients with a history of transient ischemic attack (TIA) or stroke
- Prasugrel and clopidogrel users' prior history compared



#### Clopidogrel and Prasugrel: Prior Stroke or TIA



Clopidogrel (153,191)*	25,820	11,815
Prasugrel (6,997)	540	134

\* New users after <a>>265</a> day washout

info@mini-sentinel.org



#### Conclusions / Limitations

- Some prasugrel users have a prior diagnosis of TIA or stroke
  - Fewer than for clopidogrel users
- ICD-9 codes used for TIA and stroke not validated in Mini-Sentinel
- Longest look back for event was 1 year, patients that had an event >1 year prior would be missed



#### Active surveillance activities

Characterize population and treatments

#### For older products, rapidly assess concerns arising from any source



#### Rapid Queries of Exposure-Outcome Pairs

- Angiotensin receptor blockers (ARBs) and celiac disease
- Drugs for smoking cessation and cardiac outcomes
- Drugs for Parkinson's disease and acute myocardial infarction or stroke
- Analeptics and severe cutaneous adverse reactions
- Oral hypoglycemics and hypersensitivity reactions
- Atypical antipsychotics and hypersensitivity reactions
- Vascular endothelial growth factor (VEGF) inhibitors and osteonecrosis of the jaw
- Direct thrombin inhibitors / warfarin and hemorrhage
- Aspirin antagonists and stroke or transient ischemic attack



#### ARBs and celiac disease

# Potential olmesartan signal identified in AERS database

Review of cases inconclusive



#### ARBs and celiac disease



\_ARBs: New users after <u>></u>365 day washout; Celiac Disease: 1st dx code after >365 day without diagnosis.

info@mini-sentinel.org



#### Limitations

- □ Capture of relevant GI events may be incomplete
- Potential inclusion of irrelevant events
- Patients exposed to different agents may differ with respect to risk of GI symptoms
- Majority of exposures limited to a few months duration
- Observed risk doesn't exclude excess



#### ARBs and celiac disease

#### i-sentinel.org/work\_p × + S www.mini-sentinel.org/work\_products/Assessments/Mini-Sentinel\_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease.pdf BA 👸 WP S Brkin S Post 🕒 Sabin 🕒 Gillick 🞯 HMS 🎬 TAP 🏹 Grnwld tds DmStrt 🧮 👸 Kr 🕎 🕒 Dgb 🐼 NYR 🛤 Sox 🔊 Google Reader 🚺 Netflix 📟 NextBus 🚱 Bookmarks

**Modular Program Type**: MP 3 - Drug Use – Incident Outcomes (See online specification for details: http://www.mini-sentinel.org/data\_activities/details.aspx?ID=111)

#### **Date Posted:**

#### Medical product exposures of interest:

This Modular Program execution included 7 unique exposures, all in the Angiotensin II Receptor Blocker (ARB) drug category. The exposures were defined using National Drug Codes (NDCs identified by FirstDataBank), limited to the oral formulations, identified in the Mini-Sentinel outpatient dispensing file. The 7 drugs included were:

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan



#### One-Time Protocol-based Assessments

- Rotavirus Vaccines and Intussusception
- Influenza Vaccine and Febrile Seizures
- Influenza Vaccine and Pregnancy Outcomes
- HPV4 vaccine and Venous thromboembolism
- ACEIs/ARBs/aliskiren and Angioedema
- Aripiprazole and Venous thromboembolism



#### **Rotavirus Vaccines and Intussusception\***

Vaccine doses in study
Individuals in study
Number of outcomes based
on ICD9 codes
1.8 million
465,000
64 cases within 21d
after any vaccine dose

\* Numbers are for RotaTeq. Estimates are based on actual numbers from the first two data partners and inference for the third data partner.

info@mini-sentinel.org



#### HPV4 vaccine and Venous Thromboembolism\*

Vaccine doses in study
Individuals in study
Number of outcomes based
Individuals in 28d
after any vaccine dose

\*HPV4 vaccine is Gardasil. Estimates are based on inferences from preliminary data characterization analyses.

info@mini-sentinel.org



#### Influenza Vaccines and Febrile Seizures\*

Vaccine doses in study 860,000 first doses
Individuals in study 860,000
Number of outcomes based 91 cases within 1d after on ICD9 codes a vaccine dose

\* Estimates are for 6-59 mo olds, based on inferences from preliminary data characterization analyses.



#### Active surveillance activities

- Characterize population and treatments
- For older products, rapidly assess concerns arising from any source
- Monitor impact of FDA actions



#### Assessments of FDA's Regulatory Actions

#### Long Acting Beta Agonists

<u>Objective</u>: Evaluate the impact of labeling change advising against long term use of LABAs as a single agent on changes in use and health outcomes of interest <u>Status</u>: Workgroup developing protocol



#### Active surveillance activities

- Characterize population and treatments
- For older products, rapidly assess concerns arising from any source
- Monitor impact of FDA actions
- For new products, monitor accumulating experience for pre-specified potential adverse outcomes



#### Antidiabetic Drugs and Acute MI

- Repeated evaluation of acute MI risk in new users of saxagliptin vs. comparator antidiabetic drugs
- Case mix adjustment via disease risk scores and propensity scores
- 280,745 eligible new users Aug, 2009 Dec, 2010:

Antidiabetic drug	New users
Saxagliptin	5,877
Sitagliptin	31,425
Pioglitazone	55,134
Long-acting insulin	72,024
2 <sup>nd</sup> generation sulfonylureas	116,285



#### Challenges

- Many different exposures
- Many different outcomes
- Many patient types
- Many and diverse data environments
- Need for timeliness in both detection and followup
- Need to avoid false alarms
- Need for multiple simultaneous activities
- Need for surge capacity





#### The NEW ENGLAND JOURNAL of MEDICINE

February 10, 2011. Volume 364: 498-9

# Perspective

# Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

> The Food and Drug Administration (FDA) now has the capacity to "query" the electronic health information of more than 60 million people, posing specific questions in order to monitor the safety of

convening an ongoing series of discussions among stakeholders to address the near- and long-term challenges inherent in implementing the Sentinel System.<sup>3</sup> In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role

approved medical products. This information to answer additional



# Thank you!