Highlights from the Fifth Annual Sentinel Initiative Public Workshop

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March 7, 2013
Welcome and Overview

Housekeeping:
• To minimize feedback, please confirm that the microphone on your telephone is muted.
• To mute your phone, press the mute button or ‘*6’. (To un-mute, press ‘*7’)
• There will be opportunities for questions and discussion at the end of today’s presentations. **Please use the Q & A tab on the top of your screen to submit your questions into the queue at any point** and we will call upon you to state your question.
• Call the Level 3 Conferencing at 1-888-447-1119 with technical problems.
Progress and Future Directions of the Sentinel Initiative

Patrick Archdeacon, MD
Medical Officer
Office of Medical Policy/CDER/FDA
March 7, 2013
FDA Amendments Act of 2007
Section 905: Active Postmarket Risk Identification and Analysis

• Establish a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including
  – at least 25,000,000 patients by July 1, 2010
  – at least 100,000,000 patients by July 1, 2012

• Access a variety of sources, including
  – Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs)
  – Private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data)
Mini-Sentinel Achievements

• Protocol based one time assessments: RAAS drugs and angioedema; Gardisil and VTE
• Protocol based repeated assessments: Diabetes drugs and AMI
• Modular program based one-time assessments: Dabigatran, warfarin & GI bleed, intracerebral hemorrhage

To date, Mini-Sentinel has focused on analyzing data to test existing hypotheses, either through resource-intensive protocol based studies or rapid (if potentially confounded) modular program assessments.
At Present
• Infrastructure in place to capture product exposures
• Some experience in measuring a few outcomes (AMI, bleeding)
• Sufficient expertise available to develop programming compatible with CDM to apply existing methodologies to specific product:outcome pairs
• More rapid modular programs have limited ability to control for confounding

Goal Capacities
• Increase current capabilities
  But also…
• Create semi-automated routine surveillance capability
  - Need vastly expanded menu of measurable outcomes
  - Need adaptable programs that can apply general methodologies to many product:outcome pairs
  - Need improved understanding of appropriate application of statistical and epidemiology tools in this setting to mitigate systematic bias

- Highly specialized system that supports important but restricted range of activities
- Comprehensive system capable of full range of safety surveillance
**Goal: 1st Iteration of Routine Surveillance System by June 2013**

### Features
- Ability to select from a menu of HOIs
- Will leverage existing MSDD to evaluate associations between drugs/biologics/vaccines and HOIs
- Employ different methodologies based on product-HOI pair

### Gaps
- Not all HOIs will have been validated within MSDD
- Will not have capability to examine associations between most device-HOI pairs
- Methodologies and data use policies will continue to evolve with experience
• For newly approved products, the system will look for associations with a restricted set of HOIs through semi-automated queries of the MSDD.

• The set of HOIs for a given product will be selected at the Center level from a menu of possible HOIs.
Activities Required to Meet Goal

1) Establish algorithms capable of identifying relevant HOIs (and also confounders and cohorts) within the MSDD

2) Create new modules capable of replicating features of basic epidemiologic study designs

3) Develop data use strategies, refine policies, and create implementation tools
HOIs with Algorithms under Development

- Pulmonary Fibrosis
- Severe Acute Liver Injury
- Anaphylaxis
- Acute Kidney Injury
- Acute Myocardial Infarction
- GI Bleed
- Hypertensive Emergency
- Premature Delivery
- Neutropenia
- Agranulocytosis
- VTE
- Asthma Exacerbation
- Sepsis
- Tuberculosis
- EMM/SJS/TENs
- Guillain Barre Syndrome

- Aplastic Anemia
- Bell’s Palsy
- Stillbirth/Spontaneous Abortion
- Acute Pancreatitis
- Ischemic Stroke
- Hemorrhagic Stroke
- Acute Respiratory Failure
- Juvenile Rheumatoid Arthritis
- Deafness
- Systemic Lupus Erythematosus
- Thrombocytopenia
- TTP
- Inflammatory Bowel Disease
- Peripheral Neuropathy

- Pulmonary Hypertension
- Hip Fracture
- Rhabdomyolysis
- Sudden Cardiac Death
- Tendon Rupture
- Type 1 Diabetes
- Seizure, febrile
- Suicide, including attempted suicide
- Valvulopathy
- ITP
Mini-Sentinel also Developing Algorithms to Identify Cohorts

- Nursing home residents
- Pregnant women
- Live births
- Babies born prematurely
- Immunocompromised patients
- Patients who received fluoroquinolones for PEP
- Asthmatics
- Smokers
- Patients with CAD
- First Responders
- Patients with Obesity
- Patients with ESRD
- Patients with dementia
- Patients with mood disorder
- Diabetics
Activities to Develop Analytic Modular Programs for Routine Surveillance

For each epidemiologic design, a modular program will be built and tested using example datasets for selected positive and negative controls. The selection of these three designs was informed by the prior work of the Taxonomy workgroup.

<table>
<thead>
<tr>
<th>Module 1</th>
<th>Module 2</th>
<th>Module 3</th>
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<tbody>
<tr>
<td><strong>Self-controlled case series</strong></td>
<td><strong>Cohort approach 1</strong></td>
<td><strong>Cohort approach 2</strong></td>
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<tr>
<td>Parameters:</td>
<td>Parameters:</td>
<td>Parameters:</td>
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<tr>
<td>- Exposure time trend adjustment</td>
<td>- Score-based matching (PS, DRS)</td>
<td>- Regression</td>
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<tr>
<td>- ...</td>
<td>- fixed/variable ratio</td>
<td>- Weighted or unweighted</td>
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<tr>
<td>Maclure et al. PDS 2012</td>
<td>Rassen et al. AJE 2011, PDS 2012; Snchez et al. Epidemiol 2009; Glynn et al PDS 2012; Austin et al Stat Med 2011</td>
<td>...</td>
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Wang et al. Epidemiology 2011
Musonda et al. Vaccine 2008
Additional Tasks Required to Support Routine Surveillance

• Determine appropriate uses of preliminary vs finalized administrative data for optimizing “near real time” surveillance

• Determine appropriate policies regarding data use and re-use in the context of routine surveillance

• Develop operations manual to guide end-user application of routine surveillance tools
Protocol-Based Evaluations vs Semi-Automated Surveillance

**Protocol-Based**
- More resource intensive
- Greater control of systematic biases
- Typically one time analysis
- Ability to test hypotheses

**Semi-Automated**
- Less resource intensive
- Less control of systematic biases
- Sequential analyses
- Ability to generate hypotheses
Current Mini-Sentinel (MS) Pilot
Sept 2009 - Sept 2014
Contract includes:
- Data Core
- Methods Core
- Protocol Core
- Operations Center

National Resource Data Infrastructure
Awarded in Sept 2013

Methodological Research For Medical Product Surveillance Using Electronic Healthcare Databases
Awarded in Sept 2013

Sentinel Operations Center
Awarded in Jan 2014
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

March 7, 2013
Mini-Sentinel in brief

- Congress mandated FDA develop a safety surveillance system based on electronic health data
- Mini-Sentinel is a five year pilot program. Its goals:
  - Develop capacity for active medical product safety surveillance using existing automated healthcare data
  - Develop and evaluate scientific methods
  - Allow FDA to evaluate safety issues
  - Assess barriers and challenges
- Mini-Sentinel recently entered its fourth year
Mini-Sentinel partner organizations

~400 investigators
Mini-Sentinel distributed analysis

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
“This assessment [...] FDA’s Mini-Sentinel pilot...”
Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn McCloskey, MD, MPH; Azadeh Shoaibi, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD
“...we commend the Food and Drug Administration for developing the Mini-Sentinel...”

Risks and Benefits of Medications in Real-World Practice

All drugs have adverse effects. The challenge for practicing physicians is to determine which medications have the fewest adverse effects for a given therapeutic benefit. Unfortunately, drugs with similar indications often have not been directly compared with one another because their approvals were based on comparison with placebo or with only one member of the same or a similar class. Moreover, the comparable risks for unusual adverse effects with a group of different medications having similar indications can be even more challenging because most phase 3 efficacy trials are not powered to accurately estimate or even detect the inverse effect that can be life-threatening. Using the Food and Drug Administration's Mini-Sentinel program, Toh et al show that all the drugs acting on this system are not associated with the same incidence of angioedema. Specifically, the incidence was significantly higher for angiotensin-converting enzyme inhibitors and aliskiren than for angiotensin receptor blockers, and all the study drugs were associated with a greater incidence of angioedema compared with the reference category of β-blockers.

Beyond the content, we commend the Food and Drug Administration for developing the Mini-Sentinel Distributed Database; this analysis draws on medication use and...
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
A Mini-Sentinel week

- Distributed dataset development/maintenance
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Data Refreshes and Standard Data Checks

- 120+ core data refreshes received to date
- 100+ tables per data partner per refresh
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular programs development / use to address “standard” questions
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
Typical input to modular programs

- **Start Date**
  - Look back XX days
  - Inclusion/exclusion condition

- **Index Date**

- **End Date**
  - Outcome(s)
  - Optional: blackout days
  - Optional: extension days

- **Start of new treatment episode**

- **Time**
This assessment [...] FDA’s Mini-Sentinel pilot...
Use of modular programs

- MP Queries
- MP Reports
- MP Scenarios
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development/use
- Protocol development / implementation to address unique types of questions
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System

Sengwee Toh, ScD; Marsha E. Reichman, PhD; Monika Houstoun, PharmD; Mary Ross Southworth, PharmD; Xiao Ding, PhD; Adrian F. Hernandez, MD; Mark Levenson, PhD; Lingling Li, PhD; Carolyn Mccloskey, MD, MPH; Azadeh Shoaii, MS, MHS; Eileen Wu, PharmD; Gwen Zornberg, MD, MS, ScD; Sean Hennessy, PharmD, PhD
Overarching goals of the project

- Assess selected drug-event associations
  - Drugs targeting renin-angiotensin-aldosterone system & angioedema

- Build general strategies for safety assessments of medical products on the market for >2 years

- NOT designed to provide definitive evidence of a causal relation
Process to conducting a MS protocol-based assessment

- FDA identifies topic
Cohort creation

Total population in Mini-Sentinel as July 2011
~99,000,000

Applying eligibility criteria
(age, medical history, etc)

ACEIs 1,845,138
ARBs 467,313
Aliskiren 4,867
ß-blockers 1,592,278
Statistical analysis

- Propensity score approach
  - Condensing information from a large number of variables into a non-identifiable measure

- Case-centered approach and meta-analysis
  - Needing only aggregated data to complete the analysis
Timeline

- Kick-off meeting
- Protocol finalized
- 1st workplan sent
- Analysis complete
- Draft final report

Mar 11 | Aug 11 | Sep 11 | Jan 12 | Feb 12

Total time from start to completion: ~11 months
Results

Toh et al, Arch Intern Med 2012;172:1582-1589

* Beta-blockers as the common reference group
Summary of overarching goal #1

- Largest assessment on this topic to date

- Replicated known ACEIs–angioedema association
  - With much more precise risk estimates

- Provided new information on angioedema risk for
  - Aliskiren (caveat: based on 7 exposed cases)
  - ARBs
Summary of overarching goal #2

- Developed a time and cost efficient process to perform medical product safety assessments within a large distributed data system

- Developed analytic strategies to perform robust statistical analysis without sharing identifiable information
Reviewing medical records

- Claims data are reliable for some diagnoses and many exposures
- Medical records are sometimes needed to
  - Adjudicate case status
  - Confirm exposure to product of interest
- Mini-Sentinel can obtain relevant parts of selected records
  - Data partners obtain relevant sections of records, redact identifying information, forward de-identified material to expert adjudicating panel
  - Expert panel applies standard definitions to classify case status, assesses accuracy of exposure data
Rotavirus vaccines and intussusception

- Rotavirus vaccines are live, attenuated, oral vaccines

- Rotashield
  - Licensed in August 1998
  - In 1999, Rotashield voluntarily withdrawn due to increased risk of intussusception
  - Excess risk: 1-2 cases/10,000 vaccine recipients

- RotaTeq (2006) and Rotarix (2008) licensed after clinical trials with >60,000 infants

- Need to confirm both intussusception case status and vaccine exposure
Rotavirus vaccine doses through 6/2011

<table>
<thead>
<tr>
<th></th>
<th>1st doses</th>
<th>All doses</th>
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<tbody>
<tr>
<td>RotaTeq</td>
<td>507,874</td>
<td>1,277,556</td>
</tr>
<tr>
<td>Rotarix</td>
<td>53,638</td>
<td>103,098</td>
</tr>
</tbody>
</table>
Case identification

Potential cases identified in claims data = 343

Chart obtained = 267 (78%)

Confirmed intussusception = 124 (46%)

Cases are from whole infant population and include unexposed
Protocols in the field now

- Rotavirus vaccine and intussusception
- Impact of labeling change on use of long acting beta agonists
- Human papillomavirus vaccine and thromboembolism
- Anti-diabetic drugs and acute myocardial infarction
Protocols under development

- Influenza vaccine safety (same season, sequential analysis)
- Metabolic effects of atypical antipsychotics in children and adolescents
- Influenza vaccine and febrile seizures
- Dabigatran and stroke / bleeding
- Influenza vaccine and birth defects, spontaneous abortion
- IV iron products and anaphylactoid reactions
- IV immune globulins and thromboembolic events
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development /use
- Protocol development / implementation
- **Methods development / implementation**
- Develop new capacity
- Contribute to establishing a national resource for evidence development
Methods

- Implementing routine prospective surveillance of new products using sequential methods
- Improving confounder adjustment
- Validation of health outcomes of interest
- Data mining for vaccine adverse events
Prospective surveillance at a glance

1. Newly marketed product
2. Define exposures, outcomes, etc
3. Choose analysis approach
4. Estimate the risk
5. Aggregate results over time
6. Apply alerting rules
7. Report to FDA
   FDA reports to public when appropriate
Prospective surveillance: estimate risk

Newly marketed product

Define exposures, outcomes, etc

Choose analysis approach

Risk estimation

Module 1
Self-controlled

Module 2
Cohort matching

Module 3
Cohort regression
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
Coming in 2013

- Prospective surveillance of new products
- New query tools
- New bandwidth to respond to more queries
- New data
  - Links to state birth and immunization registries
  - Explore use of inpatient data
A Mini-Sentinel week

- Distributed dataset development/maintenance
- Modular program development /use
- Protocol development / implementation
- Methods development / implementation
- Develop new capacity
- Contribute to establishing a national resource for evidence development
External engagements

- Observational Medical Outcomes Partnership
- NIH Health Care System Research Collaboratory
- Clinical Trials Transformation Initiative
- ONC Standards & Interoperability Framework (Query Health)
- IOM Roundtable on Value and Science-Driven Health Care
- Academy Health EDM Forum
- Other new partners as opportunities present
NIH Health Care Systems
Research Collaboratory

Home of the NIH Distributed Research Network
Millions of people. Strong collaborations. Privacy first.

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems

The Collaboratory
Multiple networks sharing infrastructure

- Partner Organizations can choose to participate in multiple networks
- Networks can leverage existing data, query tools, program libraries
In conclusion
Key contributors to Mini-Sentinel’s progress

- Close, frequent, coordinated interactions between FDA, data partners, content experts, epidemiologists, and statisticians
- Distributed data network
- Public health practice
- Focus on defined populations with sufficiently complete data
  - First: Claims and administrative data, plus access to full text records
  - Then: electronic medical records, registries, ...
- Rapid cycle development of capabilities
- Ability to respond quickly to predefined needs
Costs and benefits

- Up to date distributed database + hundreds of rapid response queries
- Protocol based study
- Being prepared for pandemic or other crisis

~$10 million per year
$225,000+
Priceless!
Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to support and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products.

Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.

Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise.
Thank you!
Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:
http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx