Sentinel Journey from Safety Question to Regulatory Action

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent the policies of the U.S. Food and Drug Administration.
First, some background....
FDA regulates drugs and...

- **Food**
- **Vaccines, Blood & Biologics**
- **Medical Devices**
- **DRUGS**
- **Tobacco Products**
- **Cosmetics**
- **Radiation-Emitting Products**
- **Animal & Veterinary**

Safe and Effective

Sentinel Initiative spans multiple centers...
Center for Drug Evaluation and Research
Office of Biostatistics

Over 170 statisticians across 8 divisions,
Expertise in regulatory statistics in all phases of drug development across many drug therapeutic areas

Office of Biostatistics Regulatory Science Day, September 2014
Safety in (New) Drug Development

Drug Reasonably Safe for use in Humans

Basic Research
Discovery
Preclinical

Randomized Clinical Trials

Marketing Application and Review of Benefits and Risks

Post-Market Assessments

Safety Profile of The Drug

Safety Surveillance

Why Post-Market Assessment? Example, Dabigatran

Approved on 10/2010 to reduce the risk of stroke in patients with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>PRADAXA 150 mg twice daily</th>
<th>Warfarin</th>
<th>Hazard ratio vs. warfarin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>6076</td>
<td>6022</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>123</td>
<td>187</td>
<td>0.64 (0.51, 0.81)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>104</td>
<td>134</td>
<td>0.76 (0.59, 0.98)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>12</td>
<td>45</td>
<td>0.26 (0.14, 0.49)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>13</td>
<td>21</td>
<td>0.61 (0.30, 1.21)</td>
</tr>
</tbody>
</table>

How will the 2-3 million people in US with atrial fibrillation fare on this drug?

Source: Pradaxa label, RE-LY Study

*Patients contributed multiple events and events were counted in multiple categories.
Post-Market Safety Assessment Data Include...

- Post-market randomized studies, observational studies and meta-analyses

- FDA adverse reporting system (FAERS)

- FDA led observational studies*
  - With Sentinel
  - With SafeRx/federal data partners (CMS, DoD, VA)

*Section 905 of Food and Drug Administration Amendments Acts (09/2007)
Sentinel and Mini-Sentinel
Acknowledgments

My team in the Div. of Biometrics 7 is involved in ongoing projects investigating the safety of newly approved anticoagulants discussed today. However, most projects discussed today were initiated and/or completed prior to my involvement.

- Special thanks to: Rongmei Zhang (DB7), Mark Levenson (DB7), Marsha Reichman (OSE), Mary-Ross Southworth (OND)
Take Home Messages

• Sentinel is an active surveillance system, one of many sources of safety data at FDA

• Mini-sentinel pilot implemented a structure to query sentinel and demonstrated its use

• Some methodological challenges lie ahead in post-market safety (Big data/rare outcomes, stratification, sequential analyses)
Vision and Pilot

- National safety *active* surveillance system of drugs and medical products *post-marketing*
- Results of safety *queries* are shared publically
- 48 million people currently accruing new data - 358 million person-years of observation time of drugs and vaccines
- Safety questions, protocols and results in mini-sentinel website
Sentinel System, Distributed Database

1. FDA sends safety question.
2. Coordinating Center sends analysis.
3. Data partners provide summary results.
4. Coordinating Center reviews and aggregates findings, and sends summary results.
5. FDA communicates findings to inform health care decisions.

A. Only those academic institutions with electronic healthcare data will receive safety questions for evaluation.
B. Data partners will provide summary results from analyses conducted within their secure data environments. Those summary results will not include directly identifiable health information.
Safety Question:
Drug exposure(s) (test/comparator), outcome(s), and population of interest

Statistical Inference Question: Estimation, detect or rule out risk

Feasibility of safety assessment? Generalizability to population at risk?

Not Every Safety Question is Feasible in Sentinel

Data: Electronic Healthcare Data

See FDA Guidance*

Mini-Sentinel Modular Program, Available Tools

Level 1 Request  Level 2 Request  Level 3 Request

CIDA
Cohort Identification and Descriptive Analysis
Combined functionality of Modular Programs and Analytic Tools developed in 4.10 Workgroup

PSM
Propensity Score Matching

SCRi
Self-Controlled Risk Interval

GEE
Generalized Estimating Equations

IPTW
Inverse Probability of Treatment

Binomial maxSPRT
Maximized Sequential Probability Ratio Testing

Cohort Identification and Descriptive Analysis Tools

Analytic Adjustment Tools

Sequential Analysis and Signaling Tools

Next, more methods? More diagnostics and sensitivity analyses?
Mini-sentinel, Distributed Database

- In each site
  - Control for confounding
  - Subgroup analyses
- Across sites
  - Stratified analyses of pooled results
- Data refresh quarterly

heterogeneity across sites? in time?

Source of logos: Rich Platt’s slide at mini-sentinel meeting in February 2015
The Role of the Division of Biometrics in FDA led Projects

- Develop protocol and statistical analysis plans
- [Conduct Analyses]
- Review and interpret results
- Participate in methodology working groups, e.g.
  - Sentinel Survival
  - Sentinel Prospective Monitoring Tools (PROMPT) Enhancement
<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval of Dabigatran</td>
<td>10/2010</td>
</tr>
<tr>
<td>Approval of Rivaroxaban</td>
<td>11/2010</td>
</tr>
<tr>
<td>Approval of Apixaban</td>
<td>12/2012</td>
</tr>
<tr>
<td>Reports Of bleeding (FAERS and literature)</td>
<td></td>
</tr>
<tr>
<td>Mini-sentinel (level 1) investigation</td>
<td>10/2012</td>
</tr>
<tr>
<td>Drug Safety Communication (12/2011) and change in labeling (01/2012)</td>
<td></td>
</tr>
<tr>
<td>Drug Safety Communication (11/2012) and NEJM publication</td>
<td></td>
</tr>
</tbody>
</table>

NISS Spring Affiliates Meeting, March 15th 2015
Dabigatran Example (continued)

Safety Question
• Population of interest: subjects with atrial fibrillation (2-3 millions Americans)
• Exposure: Dabigatran versus Warfarin (anticoagulants)
• Outcomes:
  – Stroke
  – Serious bleeding

Electronic Claims Data
• Cohort: AF diagnosis and new filled prescription of dabigatran or warfarin, other inclusion/exclusion
• Outcomes identified with ICD-9 codes positive predictive values > 80% for most outcomes
Level 1: identifies cohorts of interest and, for some cohorts, can perform descriptive analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>10,599</td>
<td>16</td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>12,195</td>
<td>19</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>10,587</td>
<td>8</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>12,182</td>
<td>10</td>
</tr>
</tbody>
</table>

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

"...large numbers of reported cases of bleeding with dabigatran is an example of stimulated reporting. The Mini-Sentinel assessment suggests that bleeding rates with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY”

-April 2013
Sentinel Journey – Dabigatran Example (continued)

CMS/SafeRx Protocol based Investigation
Final statistical Analysis plan (06/2013)

Mini-sentinel Rivaroxaban Protocol Based Assessment (level 3- like) (03/2014)

Mini-sentinel Protocol Based Assessment (level 2-like) (03/2014)

Drug Safety Communication based on CMS Study (05/2014)
Dabigatran Example
Protocol Based Assessment (level 2 *like* query)

**Protocol**

**Adjusted Analysis**

- New user cohort study
- Propensity score matching by site to control for confounding
- Primary analysis is time to event using cox regression stratified by site

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated with Dabigatran or Warfarin for Non-Valvular Atrial Fibrillation

Running title: Graham et al.; Comparative safety of dabigatran and warfarin

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Shih, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PharmD, MPH; Thomas E. MacCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kehan, MD, MMS

1Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 2Acumen LLC, Burlingham, CA; 3Office of Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 4Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 5Dept of Economics, Stanford University, Stanford, CA; 6Centers for Medicare & Medicaid Services, Washington, DC

Published online October 2014

“In this study...Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin.”

-May 2014
Rivaroxaban Example Protocol Based Assessment (level 3 like query)

Adjusted, Sequential Analyses

• New user cohort study

• Variable ratio propensity score matching by site to control for confounding

• Sequential looks (5) with Pocock stopping boundary

• Primary analysis is time to event using cox regression stratified by site

http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_PROMPT_Rivaroxaban-Surveillance-Plan.pdf
Sentinel – Some Regulatory Science Challenges

- Regulatory response to a safety signal, considerations of:
  - Statistical significance
  - Clinical relevance
  - Benefit-Risk
  - Speed of sharing results with public
  - Confidence in results
Take Home Messages

• Sentinel is an *active* surveillance system, one of many sources of safety data at FDA

• Mini-sentinel pilot implemented a structure to query sentinel and demonstrated its use

• Some methodological challenges lie ahead in post-market safety (*Big data/rare outcomes, stratification, sequential analyses*)
WANT TO GET INVOLVED?
IMEDS Methods

IMEDS Program

Key Areas

IMEDS will help the FDA, regulated industry, and clinicians improve patient care and the safety of medical products by focusing on three areas.

1. IMEDS-Methods
   Facilitate methods research aimed at monitoring safety of marketed medical products.

2. IMEDS-Education
   Train scientists in how to conduct methods research using electronic healthcare data.

3. IMEDS-Evaluation
   Use research findings to help understand the risks and benefits of marketed medical products.

Source: Susan Gruber slide at sentinel meeting in February 2015
To find out more...

- **Mini-sentinel website**
  http://www.mini-sentinel.org/

- **Sentinel Initiative Public Workshop**
  http://www.brookings.edu/events/2015/02/05-fda-sentinel-initiative-workshop

- **FDA/Sentinel initiative website**
  http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149341.htm

THANK YOU
Back up
Sentinel – Some Data Limitations

- Include claims data, will include more electronic medical records and lab data
- Ascertainment of exposure, drug dispensed and gaps in exposure
- Ascertainment of outcomes
- Ascertainment of confounders
- Safety outcomes are usually rare

Not Every Safety Question is Feasible in Sentinel
Sentinel – Some Design and Analyses Challenges

• Modeling rare outcomes

• Controlling and/or assessing
  – Unmeasured confounding bias
  – Confounding by indication, channeling biases
  – Selection bias

• Assessing time varying treatments and adherence

Diagnostics and sensitivity analyses are important
Sentinel – Some Design and Analyses Challenges (continued)

- Working around limit on pooling data across sites
  - Control for confounders in each site
  - Subgroup analyses in each site
  - Simple stratified analyses across sites

- Sequential testing

Assessing heterogeneity across sites and in time is important
Sentinel – Some Regulatory Science Challenges

- Regulatory response to a safety signal, considerations of
  - Statistical significance
  - Clinical relevance
  - Benefit-Risk
  - Confidence in results
  - Speed of sharing results
Safety Question:
Drug exposure(s) (test/comparator), outcome(s), and population of interest

Data: Electronic Healthcare Data

Statistical Inference
Question: Estimation, detect or rule out risk

Feasibility? Generalizability?

YES

Pre-specified Statistical Analysis Plan (SAP)

Statistical Analyses

Safety Assessment
Dabigratran, FAERS reports of Bleeding

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Year Approved</th>
<th>Direct Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DABIGATRAN</td>
<td>PRADAXA</td>
<td>2010</td>
<td>817</td>
</tr>
<tr>
<td>2</td>
<td>WARFARIN</td>
<td>COUMADIN</td>
<td>1954</td>
<td>490</td>
</tr>
<tr>
<td>3</td>
<td>LEVOFLOXACIN</td>
<td>LEVAQUIN</td>
<td>1996</td>
<td>393</td>
</tr>
<tr>
<td>4</td>
<td>CARBOPLATIN</td>
<td>N/A</td>
<td>1989</td>
<td>376</td>
</tr>
<tr>
<td>5</td>
<td>LISINOPRIL</td>
<td>ZESTRIL</td>
<td>1988</td>
<td>351</td>
</tr>
<tr>
<td></td>
<td>All other drugs</td>
<td></td>
<td></td>
<td>18,575</td>
</tr>
<tr>
<td></td>
<td>Total (all cases)</td>
<td></td>
<td></td>
<td>21,002</td>
</tr>
</tbody>
</table>

Source: Institute of Safe Medication Practice Reporting on FAERS data
Why Safety Question Post-Marketing?

• Biological plausibility of adverse event
• Pre-clinical signal
• Imbalance in clinical studies
• Safety signal in published studies
• Many adverse event reports

Safety concern due to higher risk than expected and/or rare but serious risk
Sentinel – Some Data Limitations

- Includes mostly claims data
- Ascertainment of exposure, drug dispensed and gaps in exposure
- Ascertainment of outcomes and covariates
- Control for confounding
- Safety outcomes are usually rare

Not Every Safety Question is Feasible in Sentinel

Guidance for Industry and FDA Staff
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data