How CDER is Using Mini-Sentinel Tools and Resources for Post-Marketing Safety Issues

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• CDER use of Mini-Sentinel data emphasizing Modular Programs and Summary Tables
  – Less complex than protocol based assessments
  – Rapid turnaround time

• Complementary use of Mini-Sentinel and AERS data

• Example
Use of Mini-Sentinel Tools/Resources

Process Goals:

• Include Mini-Sentinel tools/resources when planning for post-market drug safety related activities for newly approved drugs

• Include Mini-Sentinel tools/resources when considering how to proceed as a new drug safety issue emerges, or a previously known safety issue re-emerges or changes character.

Consider Mini-Sentinel along with other potential sources of drug safety information as part of standard procedures
Use of Mini-Sentinel Tools/Resources
In Addition...

• In some cases examine data related to safety issues not currently active in order to:
  – Provide additional information
  – Explore the capabilities and opportunities provided by Mini-Sentinel data and infrastructure

• ALL queries are being posted
Applicability of Mini-Sentinel Tools/Resources

• Can we assess exposure?
• Do we have reasonable algorithm for outcome?
• Look at structure of safety issue:
  – Can current modular programs address the issue?
  – Do we need to enhance a modular program?
  – Is the issue complex enough to require/benefit from a protocol based assessment?
• Timing / urgency / priority
• Run a Summary Table / Modular Program to determine exposure across Mini-Sentinel Data Partners
Components of a Comprehensive Post-marketing Surveillance Program at CDER

- **Drug Utilization data:**
  - Sales
  - Outpatient
  - Inpatient

- **Passive Surveillance**

- **Pharmacoepidemiologic Studies**

- **Active Surveillance**

- **Integrated Safety Review**
Potential Role of Mini-Sentinel After AERS Identification of Potential Signal

• Rationale: AERS potential signal for an event
• Due to this finding we can use a Modular Program query to get rapid information
• Results could:
  – Indicate no difference between event rates for drug of interest and comparators
  – Indicate difference that required follow-up within Mini-Sentinel or through other data sources
  – Indicate need for continued routine surveillance
Power of Complementary Surveillance Tools

- **Standard Modular Program limitations**
  - Lack of adjustment for confounding
  - Algorithms for outcomes

- **Standard AERS limitations**
  - Lack of denominators
  - Potential biases/influences in reporting

- **Iterative relationship between data from AERS and from Mini-Sentinel**
  - Adjust modular programs to take into account characteristics reported in AERS
    - Pre-existing conditions
    - Latent period of exposure prior to outcomes being reported
    - Concomitant drug use
Power of Complementary Surveillance Tools

• AERS has the ability to identify a rare event that requires someone to observe and report an event.

• Mini-Sentinel data provides observational data, can give rates of events, but in general need to know the outcome to be assessed.

• These are also supplemented with other data sources.

• Weight given to evidence from various sources depends on individual circumstances.
Gastrointestinal and Intracranial Hemorrhage in New Users of Dabigatran and Warfarin: Mini-Sentinel Distributed Database
Dabigatran

- Approved October 19, 2010 indication of non-valvular atrial fibrillation
- Anticipating a protocol based assessment in Mini-Sentinel at time of approval
- Large number of AERS reports
  - Stimulated reporting in AERS is expected for drugs new to the market vs. comparators on the market for many years (Weber Effect)
  - Determine if we could use rapid query in Mini-Sentinel to put a potential bound on risk
- Modular program feature of Mini-Sentinel
ICH and GI Bleeding Outcomes/Events

• New users of dabigatran and warfarin
  – During 183 days prior to index dispensing:
    • No dispensings of either dabigatran or warfarin
    • No occurrence of ICH or GIH in in-patient or emergency room setting
    • Require a diagnosis of atrial fibrillation in any healthcare setting

• Incidence Rate = events / 100,000 days at risk

• Additional analyses
  – Define new use by single drug
  – Without the atrial fibrillation requirement
  – Using 365 days instead of 183 days
**Intracranial (ICH) and Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel (Oct 2010 – Dec 2011, Incidence Rate = New Events/100,000 Days at Risk)**

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Pre-existing Cond. Requirement</th>
<th>Warfarin</th>
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<tr>
<td>N</td>
<td>Incidence Rate</td>
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<td>10,569</td>
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<td>Atrial Fibrillation – 183 days</td>
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<td>9,216</td>
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<td>12,161</td>
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<td>10,464</td>
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<tr>
<td></td>
<td>No requirement – 365 days</td>
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### Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel
(Oct 2010 – Dec 2011, Incidence Rate = New Events/100,000 Days at Risk)

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Limitations

- No adjustment for confounding or diagnosis exclusions (e.g. joint replacement)
  - But do have pre-existing condition requirement
- Don’t have data on deaths in absence of medical billing
- Some users of drugs are not included
- Algorithms largely not validated in observational data
Summary Comments

• Currently in the second quarter of yr 4 of the MS pilot
• MS is being considered and used, when appropriate, as part of standard processes for many drug safety issues – goal is to expand consideration of MS to all issues
• Continuing enhancements and increasing capabilities
• MS data is being used in regulatory decisions as one part of data being considered
• Weight of MS data varies with individual situation
• In future, look forward to expansion of capabilities and having this pilot inform the eventual Sentinel System
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