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…

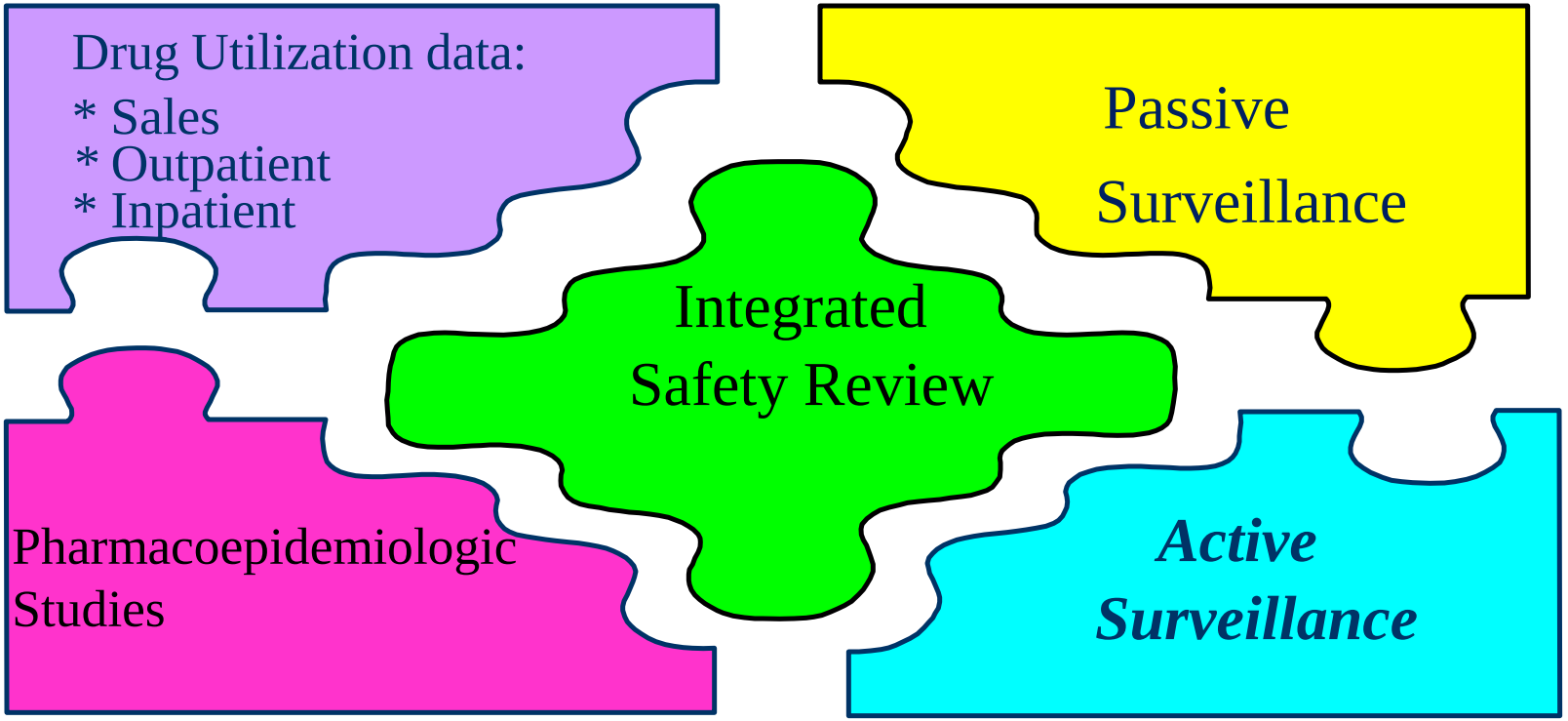
- In some cases examine data related to safety issues not currently active in order to:
  - Provide additional information
  - Explore the capabilities and opportunities provided by Mini-Sentinel data and infrastructure

- 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



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)

Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,569	2.2	Atrial Fibrillation – 183 days	43,351	5.8
9,216	2.2	Atrial Fibrillation – 365 days	34,800	6.1
12,161	2.4	No requirement – 183 days	119,470	5.0
10,464	2.5	No requirement – 365 days	97,267	5.2

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)

Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,599	1.6	Atrial Fibrillation – 183 days	43,541	3.5
9,241	1.4	Atrial Fibrillation – 365 days	34,962	3.7
12,195	1.6	No requirement – 183 days	119,940	3.1
10,493	1.6	No requirement – 365 days	97,669	3.3

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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