Sentinel Initiative: Ability of Active Surveillance to Capture Major Cardiac Adverse Events

Moni Houstoun, Pharm. D, BCPS
CDER Sentinel Initiative Coordinator
OSE/CDER/FDA

Marsha E. Reichman, Ph.D.
Scientific Lead for Surveillance Programs
CDER Lead for the Sentinel Initiative
OSE/CDER/FDA

Agenda

- Cardiac Adverse Events
- Sentinel Initiative Background
  - Active vs Passive Surveillance
  - Sentinel Initiative Goals/Objectives
  - Sentinel Initiative Pilots
- Mini Sentinel Pilot
  - Data Available to Active Surveillance, Capabilities & Limitations w Focus on Cardiac Outcomes
- Ability to Identify Sudden Cardiac Death
- Protocol Based Assessments
- Future Directions

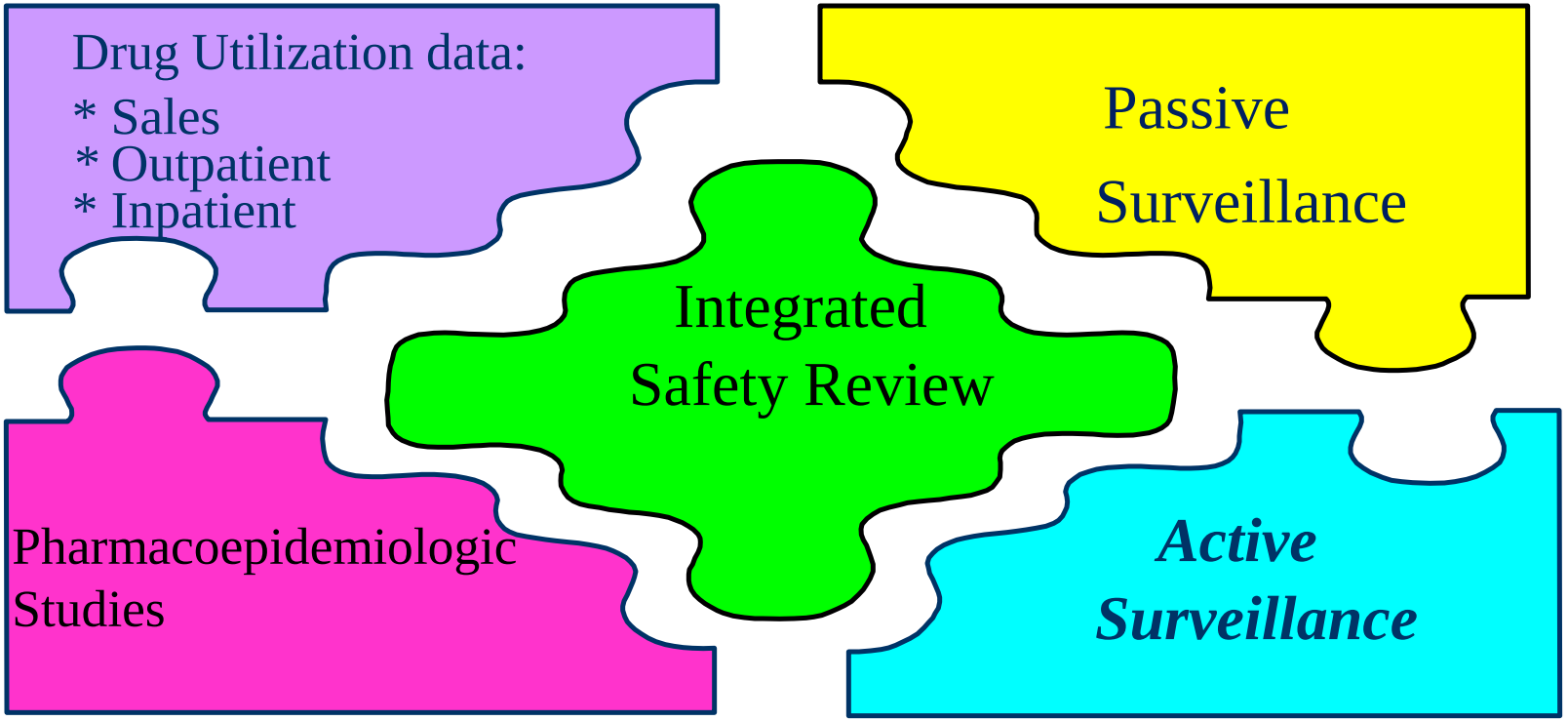
Cardiac Adverse Events (AEs)

- Sudden Cardiac Death
  - Requires more complete death ascertainment
- Acute Myocardial Infarction
  - Outcome validated in Mini-Sentinel
    - PPV 86%
  - External Validations
    - PPV 89-97%
- Heart Failure
  - Hospitalized
    - PPV 84-100%

Cardiac Adverse Events (AEs) Cont.

- Stroke
  - Ischemic stroke
    - PPV 88-95%
  - Intracerebral hemorrhage
    - PPV 89-97%
  - Intracranial hemorrhage (includes subarachnoid)
    - PPV 94%
- Ventricular Arrhythmias
  - Highly variable
    - PPV 5-100%

Components of a Comprehensive Post-marketing Surveillance Program at CDER



Active vs. Passive Surveillance

Passive Surveillance

- Only “cases” are reported
- Spontaneous reporting – cases must be either self-identified or identified by a reporting entity
- No denominators or estimates of rates
- Incomplete and non-validated data

Active Surveillance

- Both “cases” and non-cases are observed
- “Cases” are defined by objective exposure/outcome criteria
- Denominators / baseline rates of AEs are determined
- Standardized, complete, high quality data
- May allow detection of events too common for passive surveillance (MI, heart failure, etc), but rare enough to be missed in clinical trials.

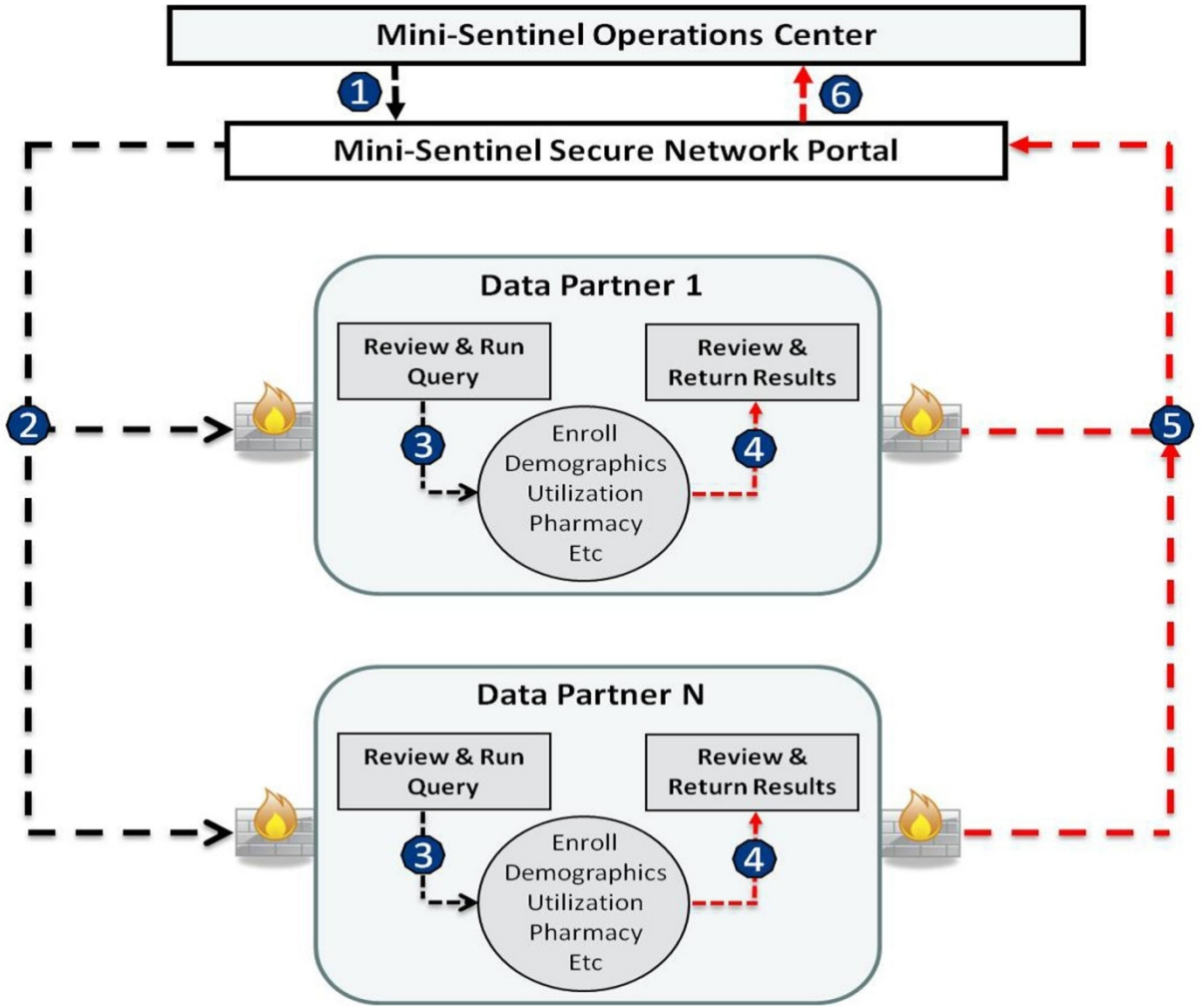
FDA Sentinel Initiative - Goals

- Develop a national electronic safety monitoring system
  - Leveraging multiple sources of currently available electronic data
  - By partnering with data holders
    - Healthcare systems, insurance companies, etc
- Enhance active post-market monitoring of medical product safety
  - More effectively look at common outcomes (e.g. MI, fractures)
  - Have denominators to easily calculate rates
  - Increase sample size with improved access to population subgroups
- Use validated design and statistical methods
- Near real-time monitoring by using a
  - Common data model
  - “Library” of tools/resources
- Integrate active surveillance with current post-market safety monitoring systems

FDA Sentinel Initiative Pilots

- **Mini Sentinel Pilot**
  - Uses privately held data
  - Data Partners: Humana, Healthcore, Aetna, Optum, HMO Research Network, Kaiser sites, Vanderbilt (Tennessee and Washington Medicaid)
  - Single data base structure at all sites
- **Federal Partner Collaboration**
  - Data from Federal Agencies: CMS Medicare, VA, DoD
  - Each agency has a different database structure
- **Both pilots use electronic medical claims and administrative data**

Mini-Sentinel Distributed Analysis



1- User creates and submits query to MSOC.

MSOC creates a computer program for data partners

2- Data partners retrieve program

3- Data partners review and run program against their local data

4- Data partners review results

5- Data partners return results via secure network to MSOC

6 MSOC aggregates results into a report for CDER/FDA

Available Data

Individual Level Data Held by Data Partners

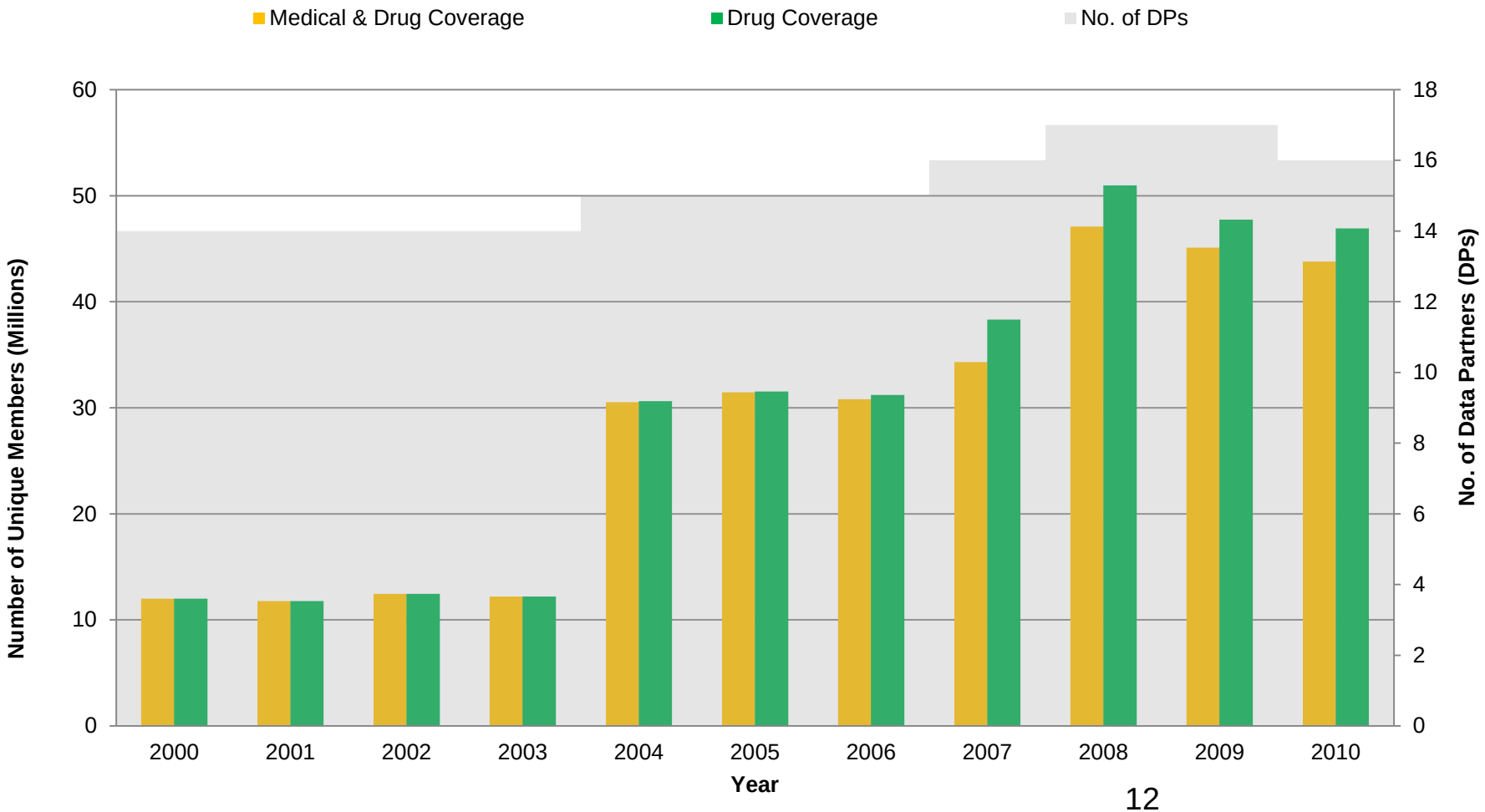
- Characteristics of People/Enrollees
  - Enrollment
    - Enrollment period start and end
    - Type of coverage – drug coverage, medical coverage
  - Demographic
    - Birth date, Sex,
    - (Race, Hispanic Origin – 70% Unknown)
- Drug Dispensing
  - Outpatient
    - Date, NDC, Days supplied, Amount
  - Inpatient – not available

Available Data

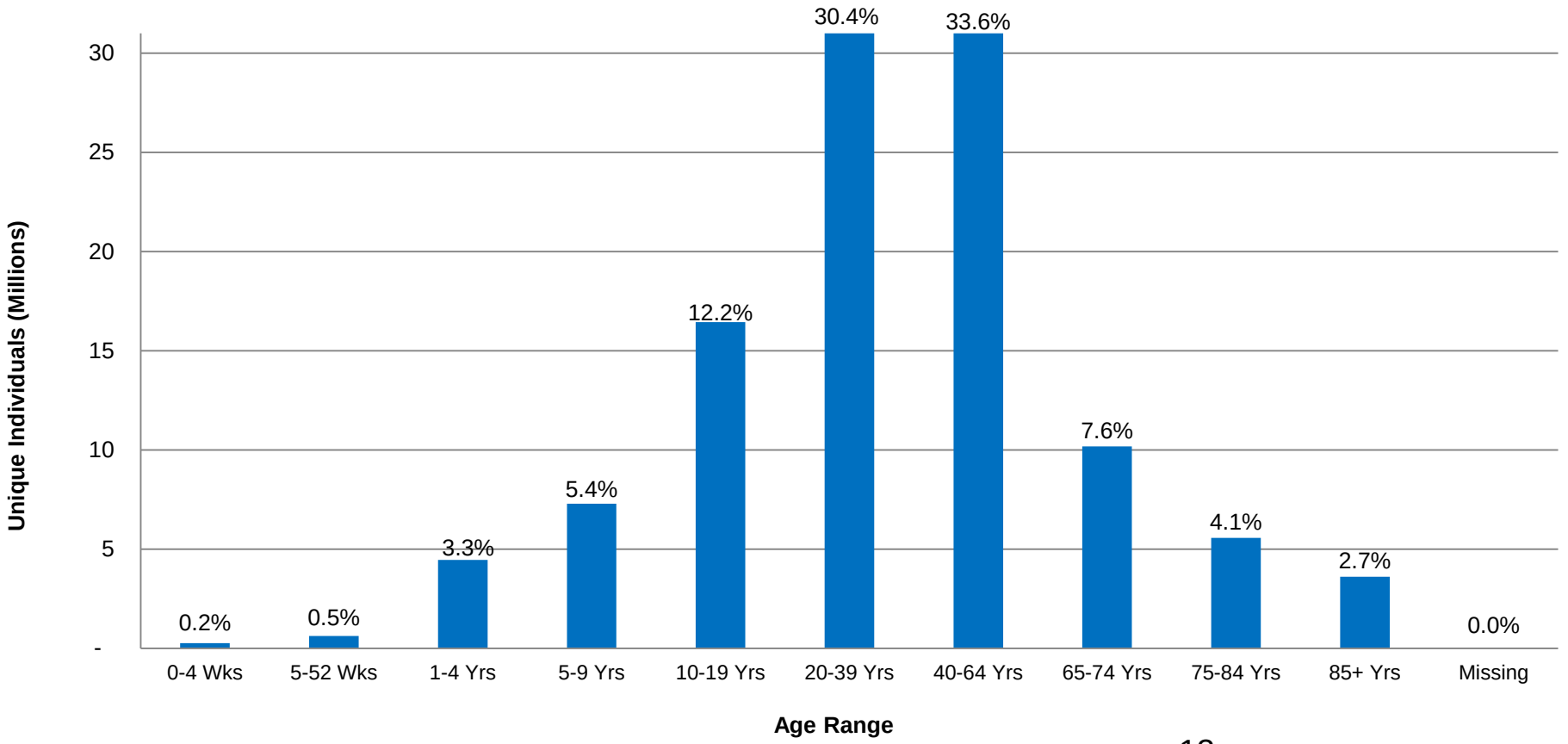
Individual Level Data Held by Data Partners

- Medical Care Utilization
  - Encounter
    - Admission/Start date, Discharge/End date, Provider, Care Setting (IP, ED, AV, etc.), Facility, etc.
  - Diagnoses
    - Date, Provider, Care Setting, Diagnosis code(s), etc.
  - Procedures
    - Date, Provider, Care Setting, Procedure code(s), etc.
- Laboratory and Vital Sign Data - being added to database where available; currently initial laboratory data is being examined for quality assurance
- Death and Cause of Death Information ?

Annual Enrollment Periods: Enrollment Type



Age Distribution



Evaluation of Sudden Cardiac Death

- Absolute requirement for information on cause of death not associated with a medical treatment claim
- Currently not using DP information of death/cause of death
  - Not timely
  - Need validation
- Best source of information on death is NDI+
  - NDI provides fact of death (100% ascertainment)
  - NDI+ provides cause of death (from state death certificates)
  - As accurate as possible
- What about linkage with NDI+?

Potential Linkage w NDI+

- Issues:
  - Logistics
    - Willingness to send data to NCHS
    - Ability to appropriately format data
    - Standardized way to match results
    - Cost
  - Currency/completeness of data
    - Currently NCHS releases a final file with 100% of state death certificates included
    - Timing – around 18 months to two years – depends on receiving all state certificates and having them properly coded with ICD-9 cause of death
    - NCHS pilot programs may make partial and eventually complete data available sooner.
  - Potential of linking Mini-Sentinel data with NDI+ is being explored
  - CMS currently has NDI+ linkage with data through 2008 – also exploring potential for updating linkages and using data

Protocol Based Assessments

- Working group of MS (or FPC) and FDA investigators developing, implementing and analyzing a protocol
- Sequential or one time surveillance
- Mini-Sentinel
  - ACEI/ARBs/Alikiren/β-blockers – Angioedema
    - Completed - results published*
  - Saxagliptin/Sitagliptin – AMI
    - sequential analysis
    - AMI algorithm validated by medical chart review
  - Dabigatran/Warfarin – Severe bleeds
    - one time analysis
    - protocol being developed

*Toh S, Reichman ME, Houstoun M, et al. Comparative Risk for Angioedema Associated With the Use of Drugs That Target the Renin-Angiotensin-Aldosterone System. *Arch Intern Med.* 2012;():1-8. doi:10.1001/archinternmed.2013.34.

Protocol Based Assessments

- Federal Partners Collaboration
  - Dronedarone/Amiodarone – Heart Failure
    - Completed
    - ICPE 2011 poster
  - Dabigatran/Warfarin – Severe bleeds
    - one time analysis
    - protocol being developed

Saxagliptin/Sitagliptin - AMI

- Comparators
  - Sitagliptin (for saxagliptin), long-acting insulin, pioglitazone, and 2nd generation sulfonylureas (glimepiride, glipizide, and glyburide)
- Sequential design
  - Saxagliptin prospective from time of approval
  - Sitagliptin retrospective, simulated sequential assessment from time of approval
- Status
  - Sitagliptin – analysis to be completed winter 2013
    - complete report ~ Spring 2013
  - Saxagliptin – last sequential “look” summer 2013
    - complete report ~ end of 2013.

Federal Partners
Dronedarone/Amiodarone: Heart Failure

- Explored the relationship between dronedarone (D) or amiodarone (A) and short-term risk (30-day) of a primary inpatient diagnosis of heart failure (HF) within the FPC
- Data from this FPC active surveillance evaluation suggested that the 30-day risk of HF is lower in incident users of D compared to A when there is no history of HF, VA or CIDs in the year prior to their first prescription.
  - However, compared to new users of D, new users of A had differences in baseline characteristics such as higher rates of medical comorbidities
  - No definitive inferences can be drawn from this evaluation as the analyses are exploratory.

Future Directions: Semi-Automated Drug Safety Assessments

- Focus on newly approved drugs
- Semi-automated assessment of uptake, use characteristics and persistence (available now)
- Semi-automated assessment of association with a set group of AEs for all new drugs, plus potential for AEs for specific NMEs, in the context of comparator drugs (available Fall 2013)
- Limited number of study designs: new user cohort, SCCS
- Some adjustment for confounding

Thank You,

For more information contact:

Monika.Houstoun@fda.hhs.gov

or

Marsha.Reichman@fda.hhs.gov

Additional Materials