US ARMY
PHARMACOVIGILANCE CENTER

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Director
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Process of Pharmacovigilance
Formulary: Safe, Effective & Favorable Risk/Benefit Ratio

**Signal Generation**

**“Rapid Analysis”**

- Signal generated by comparing study drug to comparator drug with similar indications
- Federal Partners Collaboration (FDA, DoD, VHA, CMS) A distributed system using a collaborative active surveillance protocol (incident user design): Dronedarone, Dabigatran
Data Extraction

**SOURCES**
- Claims
- Pharmacy
- DEERS
- AHLTA EHR
- Other

**REPOSITORY**
- Purchased Care ICD9, CPT, Other
- Pharmacy Data Transaction System
- Eligibility/Enrollment
- Direct Care ICD9, CPT, Other
- Labs, Vitals, Rads, Pathology, Other

**DATA MART**
- PHARMACOVIGILANCE DEFENSE APPLICATION SYSTEM (PVDAS)
- MHS Data Repository (MDR)
- CDM Clinical Data Mart
- ACTUR, DEATH
Data Cleaning and Standardization

- Direct-care diagnostic events and purchased care claims are both coded in ICD-9-CM
- All drugs are coded in NDC
- Queries can be run at any level of the ICD-9-CM hierarchy for events or the AHFS or FDB hierarchies for drugs.

### Drug Class

- **ADRENERGICS**
- **BETA-ADRENERGIC-AGENTS**
- **ANAPHYLAXIS THERAPY-AGENTS**

### Drug Sub-Class

- **METAPROTERENOL**
- **ALBUTEROL**
- **EPINEPHRINE**

### Ingredient

- **ALBUTEROL-SULFATE**
- **ALBUTEROL**

### Salt Form

- **ALBUTEROL SULFATE, 0.83MG/ML, SOLUTION, INHALATION**

### Name/Strength/Form

- **ALBUTEROL SULFATE (ALBUTEROL SULFATE), 2.5MG/3ML, VIAL-NEB, INHALATION, ROXANE LABS, 3 ml BLIST PACK**

### NDC

- **GLUCOSE**
  - 21: Glucose Monocitrate
  - 16: Glucose Monocitrate Glucovance
  - 8: Glucose Monocitrate Glucovance
  - 5997: Glucose Monocitrate Glucovance

- **GLUCOSE (POST)**
  - 1002: Glucose/Post

- **GLUCOSE (F02)**
  - 552: Glucose, Pericardial Fluid
  - 552: Glucose, Cord Blood
  - 552: Glucose, Mixed Venous

- **GLUCOSE (F07)**
  - 552: Glucose, Blood Venous
Descriptive Analysis

A descriptive analysis generates a variety of counts and other statistics for specified drugs and events occurring in a specified temporal pattern. There are four types:

• Disease Characterization Analysis: computes period prevalence for the occurrence of events of interest across the defined study period

• Drug Utilization Analysis: computes period prevalence for exposure to drugs of interest across the defined study period

• Risk-outcome Analysis: computes period prevalence and incidence rate for drugs or events of interest during a risk period that one defines based on other drugs or events. For example, you could look at the outcome of hypertension during exposure to an anti-diabetic medication, the outcome of switching to Drug B following the last exposure to Drug A, or the outcome of exposure to Drug C following a particular diagnosis

• Mother-child Analysis: identifies likely pregnancies and the child records associated with them
Exploratory Analysis

• PVDAS computes an age and gender-stratified relative risk by applying an exposure-based incident (or persistent) user cohort analysis to the drug (or drugs) of interest and a comparator (or unexposed group). Relative risk calculation is based on person-days of follow-up.
• As a comparator, you can use occurrence of the event during non-exposure to the drug or occurrence of the event during exposure to a different drug (or drugs).
• PVDAS exploratory analysis algorithm uses some of the concepts presented in the article: Brown JS et. al. Early detection of adverse drug events within population-based health networks; application of sequential testing methods. *Pharmacoepidemiology and Drug Saf.* 2007 Dec;16(12):1275-84.
Building Drug Era

The following example shows an exposure extension of 10 days added to each prescription that starts within the patient's study period. Exposures that constitute one drug era.
<table>
<thead>
<tr>
<th>DRUG OF INTEREST (DOI)</th>
<th>OUTCOME</th>
<th>COMPARATOR (C)</th>
<th>SUBSET</th>
<th>N WITH EVENT EXPOSED TO DOI (DOI N)</th>
<th>N WITH EVENT EXPOSED TO C OR UNEXP (C N)</th>
<th>N EXPOSED TO DOI</th>
<th>N EXPOSED TO C OR UNEXPOSED</th>
<th>RRISK _C</th>
<th>RRISK _B</th>
<th>RRISK _B05</th>
<th>RRISK _B95</th>
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</thead>
<tbody>
<tr>
<td>D&amp;EE</td>
<td>DVT/PE INPAT</td>
<td>unexposed</td>
<td>18-24</td>
<td>8</td>
<td>78</td>
<td>34,999</td>
<td>487,204</td>
<td>5.24</td>
<td>2.84</td>
<td>1.54</td>
<td>4.81</td>
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<tr>
<td>D&amp;EE</td>
<td>DVT/PE INPAT</td>
<td>unexposed</td>
<td>all</td>
<td>18</td>
<td>547</td>
<td>81,111</td>
<td>1,423,020</td>
<td>2.61</td>
<td>2.25</td>
<td>1.49</td>
<td>3.27</td>
</tr>
<tr>
<td>D&amp;EE</td>
<td>DVT/PE INPAT</td>
<td>unexposed</td>
<td>25-34</td>
<td>7</td>
<td>147</td>
<td>31,170</td>
<td>368,478</td>
<td>1.94</td>
<td>1.61</td>
<td>0.84</td>
<td>2.80</td>
</tr>
<tr>
<td>D&amp;EE</td>
<td>DVT/PE INPAT</td>
<td>unexposed</td>
<td>35-44</td>
<td>3</td>
<td>315</td>
<td>11,130</td>
<td>386,579</td>
<td>1.73</td>
<td>1.34</td>
<td>0.53</td>
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</tr>
<tr>
<td>D&amp;EE</td>
<td>DVT/PE INPAT</td>
<td>EE&amp;N</td>
<td>25-34</td>
<td>8</td>
<td>5</td>
<td>40,527</td>
<td>59,382</td>
<td>2.53</td>
<td>1.94</td>
<td>1.05</td>
<td>3.29</td>
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<tr>
<td>Lisinopril</td>
<td>9951:Angioedema</td>
<td>Amlodipine</td>
<td>F</td>
<td>65+</td>
<td>373</td>
<td>62</td>
<td>99,188</td>
<td>49,420</td>
<td>2.48</td>
<td>2.46</td>
<td>2.25</td>
</tr>
<tr>
<td>ACE</td>
<td>9951:Angioedema</td>
<td>CCB</td>
<td>F</td>
<td>65+</td>
<td>245</td>
<td>77</td>
<td>87,894</td>
<td>62,667</td>
<td>2.30</td>
<td>2.28</td>
<td>2.05</td>
</tr>
</tbody>
</table>
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**Signal Strengthening**

- Subgroup analysis
- Balancing patient characteristics
- Drill into patient timelines

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SIGNAL DETECTION, EVALUATION & PREVENTION
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Risk Management
Formulary Decisions & Policy: Mefloquine
Education Campaign: Know Your Dose Campaign
Identification: of drug interactions (tamoxifen and strong CYP enzyme inhibitors)

Hypothesis Testing
Full observational epidemiological study with chart review to validate endpoint
DoD MEDICATION SAFETY NOTICE

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Zonisamide (Zonegran)

On 19 Feb 2009, the Food and Drug Administration (FDA) released an FDA Alert on zonisamide (Zonegran). One of a number of newer anticonvulsants, zonisamide has been causally related to metabolic acidosis, particularly in the pediatric age group. Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults.