Strengths and Limitations of the Office of Surveillance and Epidemiology’s (OSE) Current Systems

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Office of Surveillance and Epidemiology

Pediatric Safety Surveillance Workshop
September 13, 2010
Outline

- **Background**
- Current data sources available to the Office of Surveillance and Epidemiology for pediatric safety assessment
- Description of population databases available to OSE for Pediatric Medical Product Safety and Unmet needs
- Description of Drug Use Databases and Unmet needs
- Magnitude of pediatric medical product use
- Conclusion
Provisional definition* of “signal generation”

An approach that uses statistical or review methods to identify a safety signal. No particular medical product exposure or adverse outcome is pre-specified.

*Definitions are for purpose of discussion, and are not necessarily terms or final definitions endorsed by the FDA.
Provisional definition* of “signal refinement”

A process by which an identified safety signal is further evaluated to determine whether evidence exists to support a relationship between the exposure and the outcome. Signal refinement includes assessment of whether outcomes of interest are valid.

*Definitions are for purpose of discussion, and are not necessarily terms or final definitions endorsed by the FDA.
Considerations for Pediatric Studies: Hypothesis Testing*

• Hypothesis testing* must be done with full knowledge of the number of persons exposed to the medical product of interest, and with appropriate control group(s).

• In the context of pediatric drug use, the number of persons exposed may need to be smaller than that in adult populations.

*Considerations for purpose of discussion, not necessarily endorsed by the FDA.
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Summary of Currently Available Data Sources for Pediatric Safety Studies

Signal Generation
- Adverse Event Reporting System (AERS)

Signal Refinement or Hypothesis testing
- Medicaid data (two states and 50-state)
- Department of Defense (DoD) data
- Canadian provincial data (1 province)
- Commercially insured populations (several)

Signal Refinement
- Drug Use data
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Description of Databases available to OSE for Pediatric Medical Product Safety Assessment

<table>
<thead>
<tr>
<th>Database</th>
<th>Number of reported AEs &lt;18 years*</th>
<th>Number of persons &lt;18 years*</th>
<th>Medical records available</th>
<th>Linkages to vital statistics</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERS</td>
<td>238,842 (~5% entire database that specifies age)</td>
<td>“Numerator database” Number of persons exposed not specified in database.</td>
<td>Rarely</td>
<td>No</td>
<td>Signal generation, especially with rare, serious events</td>
<td>Not suited for signal refinement or hypothesis testing</td>
</tr>
</tbody>
</table>

*Cumulative as of July 31, 2010
### Description of Databases available to OSE for Pediatric Medical Product Safety Assessment

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Medicaid (2 states: TN, WA)</td>
<td>~1.17 M (snapshot as of July, 2007)</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal refinement and hypothesis testing</td>
<td>-limited coverage (2 states)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-High turnover</td>
</tr>
<tr>
<td>Medicaid (Federal) (&lt;age 17 years)</td>
<td>~ 15 M (cumulative 1999-2009, with at least 6 month enrollment)</td>
<td>No</td>
<td>No</td>
<td>Signal generation (possibly); refinement; hypothesis testing; covers 50 states; near real time</td>
<td>-high turnover</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-limited to claims data only</td>
</tr>
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<tbody>
<tr>
<td>Department of Defense</td>
<td>~2 M (snapshot as of 3/10)</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal refinement and hypothesis testing</td>
<td>-still learning to use the data</td>
</tr>
<tr>
<td>Canadian Provincial Data (British Columbia)</td>
<td>~900,000 (snapshot as of 7/07)</td>
<td>Yes</td>
<td>Yes</td>
<td>Stable population. Signal refinement and hypothesis testing</td>
<td>-Medical practice may differ in Canada compared to U.S.?</td>
</tr>
</tbody>
</table>
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</thead>
<tbody>
<tr>
<td>HMO Research network (12 sites, commercially insured populations, &lt;24 years)</td>
<td>~1.4 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal refinement and hypothesis testing</td>
<td>-Variation between sites may be substantial</td>
</tr>
<tr>
<td>Kaiser, CA (Northern + Southern, 0-19 years)</td>
<td>~750,000</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal Refinement and hypothesis testing</td>
<td>-Not necessarily generalizable to entire US population</td>
</tr>
<tr>
<td>Healthcore (0-19 years)</td>
<td>~2 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal refinement and hypothesis testing</td>
<td>Have not yet worked with data</td>
</tr>
</tbody>
</table>

*Snapshot as of July, 2007
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<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>General Practice Research Database (United Kingdom)</td>
<td>~950,000</td>
<td>Yes</td>
<td>Yes</td>
<td>Signal refinement and hypothesis testing</td>
<td>Medical practice may differ in UK compared to US?</td>
</tr>
</tbody>
</table>

*Snapshot as of 2009
Examples of Use of Population Databases for Pediatric Studies

1. Multi-site study of drugs used to treat ADHD in children and adults and risk for serious CV events –
   – TN and WA Medicaid, Kaiser Permanente, HMO Research Network
   – Co-funded by FDA and AHRQ
   – Study will be completed in early 2011

2. Oral corticosteroid use among children in TennCare
   – Descriptive study of patient characteristics, indication and duration of use

3. Ongoing studies to examine use of antipsychotic medications in children
   – Examining indications for use and multiple potential adverse events.
   – Led by Rutgers University
   – TN Medicaid and 50-state Medicaid data set
   – Co-funded by FDA and AHRQ
   – Studies will be completed in 2011
Unmet Needs in Pediatric Safety Databases

• Better quality/depth of clinical information
  – Consistent availability of medical records
• Increased coverage of all outpatient settings
• Increased size of population covered by single database
  – Particularly databases with medical records and both numerator and denominator
• Settings appropriate for hypothesis testing of drug safety questions in children
• Tertiary care settings, rare, but serious diseases/outcomes
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FDA Drug Use Data Sources

• **Sales distribution data**
  – IMS Health, IMS National Sales Perspectives™, Retail and Non-Retail
  – Wolters Kluwer SOURCE® PHAST Institution

• **Outpatient prescription-level and patient-level data**
  – SDI Vector One®: National and Total Patient Tracker
  – Wolters Kluwer SOURCE® PHAST Prescription
  – Wolters Kluwer MarketFocus SOURCE® Lx

• **Longitudinal health care claims-level data**
  – SDI Data Extract Tool (DET)
  – IMS Health, IMS Health Plan Claims Database (PharMetrics)
  – Wolters Kluwer SOURCE® Lx

• **Physician survey data**
  – SDI Physician Drug and Diagnosis Audit™

• **Inpatient discharge billing data**
  – Premier RxMarket Advisor™
## FDA Drug Use Data Sources

### Strengths and Limitations

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales Distribution</td>
<td>Captures all major settings</td>
<td>Limited view of outpatient clinic drug utilization</td>
</tr>
<tr>
<td>Outpatient Retail Prescription</td>
<td>Nationally projected retail pharmacy, detailed dispensing analysis</td>
<td>Limited mail order and specialty pharmacy data</td>
</tr>
<tr>
<td>Longitudinal claims-level data</td>
<td>Patients tracked across continuity of care</td>
<td>Small, unprojected sample</td>
</tr>
<tr>
<td>Office-based physician survey</td>
<td>Links drug use with indication</td>
<td>Data provided as VISITS, not PATIENTS</td>
</tr>
<tr>
<td>Inpatient drug use</td>
<td>Pediatric inpatient hospital data</td>
<td>Unprojected patients, subset of pediatric hospitals</td>
</tr>
</tbody>
</table>
Unmet Needs in Drug Use Area

• Better quality/depth of clinical information
  – Nationally projected pediatric inpatient data
  – Better linkage of drug use with indications for use
  – Over-the-counter (OTC) drug utilization (patient-level)

• Increased coverage of other care settings
  – Outpatient clinics (e.g., chemotherapy, dialysis, infused therapeutic products, medical imaging and radiology)
  – OR and ED settings, specialty pharmacies, long-term care facilities, etc.
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Outpatient Retail Pharmacy Data: Total Number of Outpatient Prescriptions Dispensed to Pediatric Patients (0-17 years)


- Estimated ~28 prescriptions per 100 children in year 2009*

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>% of U.S. Population*</th>
<th>% of U.S. Outpatient Retail Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17 years</td>
<td>24.2%</td>
<td>7.5%</td>
</tr>
<tr>
<td>0-4 years</td>
<td>6.8%</td>
<td>2.0%</td>
</tr>
<tr>
<td>5-13 years</td>
<td>12.0%</td>
<td>3.5%</td>
</tr>
<tr>
<td>14-17 years</td>
<td>5.5%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

*Calculations based on U.S. Census Bureau Year 2010 Projections
There were ~827K pediatric (0-17 yrs) discharges and ~5 million adult (18+ yrs) discharges in year 2009, pediatric discharges accounted for ~14% of inpatient discharges

Limitations:

- Inpatient discharges were provided as raw counts (unprojected) from a subset within the Premier Hospital network (37 pediatric hospitals), reliable national estimates of pediatric data are currently unavailable
- Trending data is unreliable as the number of pediatric hospitals reporting into the Premier hospital network varied from 7 to 37 hospitals from years 2002 to 2009
## Five most Frequent Suspect Therapeutic Drug Classes in AERS by Age Group*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 years</td>
<td>ADHD Drugs</td>
<td>11-16 years</td>
</tr>
<tr>
<td></td>
<td>Chemotherapeutics</td>
<td>ADHD drugs</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td>Antidepressants</td>
</tr>
<tr>
<td></td>
<td>Respiratory agents</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-Acne</td>
</tr>
<tr>
<td>17-50 years</td>
<td>Antidepressants</td>
<td>&gt;50 years</td>
</tr>
<tr>
<td></td>
<td>Contraceptives</td>
<td>COX-2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Chemotherapeutics</td>
</tr>
<tr>
<td></td>
<td>Interferons</td>
<td>Osteoporosis drugs</td>
</tr>
<tr>
<td></td>
<td>Opioids</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunomodulators</td>
</tr>
</tbody>
</table>

*Pharmacoepi Drug Safety 2009;18:24-27*
Conclusions

• In general, pediatric drug safety questions cannot be adequately studied with AERS, and it is unclear whether and to what extent new databases will be able to fill the gap.

• In the post-marketing arena, the tools available in pharmacovigilance are not sufficient to precisely define either adult or pediatric drug safety problems, but are particularly not yet precise enough in children.

• We need databases that have both numerator and denominator data, have been adequately studied for validity of pediatric endpoints, have sufficient pediatric population to reach conclusions in that population.
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