FDA’s Adverse Event Surveillance Systems and MedWatch

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Purpose of Postmarketing Safety Reporting

- To learn about new risks
- To learn more about known risks
- To learn about medication errors
- To learn how patterns of use may contribute to unsafe use
- To learn about product quality problems
Sources of Drug Safety Information

Most relevant to compounded products

- Spontaneous Adverse Event Reports
- Clinical Trials
- Observational Studies
- Registries
- Clinical Pharmacology Studies
- Pharmaco-genomics Studies
- Animal Toxicology Studies
- Product Quality Reports
How Adverse Event Reports Get to FDA

Patients, consumers, and healthcare professionals

Voluntary

Manufacturer

Regulatory Requirements

FDA

FAERS Database

100% Manual Entry

92% E2B
8% Manual Entry

2.68% of all reports

97.32% of all reports*

*only includes 2013 up to 12/9/2013
# Reporting Adverse Events to FDA

<table>
<thead>
<tr>
<th>Industry</th>
<th>ICH E2B electronic standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>MedWatch 3500</td>
</tr>
<tr>
<td></td>
<td>MedWatch 3500B</td>
</tr>
</tbody>
</table>
ICH E2B Standard

- Internationally harmonized standard
- For use by industry
- About 90% of adverse event reports are through the ICH E2B standard
- May not be suitable for firms with low reports volumes
  - FDA is exploring alternative ways for manufacturers to submit reports electronically
MedWatch Form 3500

- MedWatch Form 3500
  - Designed for use by the public
  - Not consumer friendly
  - Best for healthcare professionals

- Four main elements
  - Patient
  - Product
  - Event
  - Reporter
MedWatch Form 35000A
MedWatch Form 3500A

- Designed for use by industry
- Lots of fields not present on other MedWatch forms
- Some fields are exclusively for devices
Consumer MedWatch Form

- MedWatch Form 3500B
- Introduced mid-2013
- User-friendly format for non-health care professionals
- Includes 4 minimum elements
  - Patient
  - Product
  - Event
  - Reporter
- Captures other information included on the 3500, but asks for it in a more consumer-friendly way.
Updating the MedWatch Forms

- MedWatch form has expiration dates
  - Require periodic renewal
- FDA staff determine if and how the MedWatch form needs to be changed
  - Program needs drive the changes
- Changes require extensive review
Qualities of a Good Case Report

• What makes a good case report?
  – Description of the event
  – Suspected product(s) and concomitant treatment details
  – Patient characteristics, medical history, treatment history
  – Documentation of the diagnosis
  – Clinical course and outcomes
  – Treatment and lab values at baseline, during therapy, and after therapy
  – Response to dechallenge and rechallenge
  – Any other relevant information

• This takes time

FDA Adverse Event Reporting System (FAERS)

- Computerized database
  - Informatic structure adheres to ICH standards
- Contains human drug and therapeutic biologic reports
- Adverse events, medication errors, and indications are coded to terms in Medical Dictionary for Regulatory Activities (MedDRA)
- Products are coded using the FAERS Product Dictionary
- Public extract is released quarterly
Table. Results From Quarterly Reports From January 2008 to December 2010

<table>
<thead>
<tr>
<th>Result</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential safety signals, No.</td>
<td>60</td>
<td>45</td>
<td>48</td>
<td>153</td>
</tr>
<tr>
<td>Label changes</td>
<td>30 (50)</td>
<td>28 (62)</td>
<td>16 (33)</td>
<td>74 (48)</td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>16 (53)</td>
<td>19 (68)</td>
<td>11 (69)</td>
<td>46 (62)</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>11 (37)</td>
<td>5 (18)</td>
<td>7 (44)</td>
<td>23 (31)</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Dosage and Administration</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>6 (20)</td>
<td>2 (7)</td>
<td>1 (6)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Use in Specific Populations</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>REMS</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>0</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Withdrawn from market</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Abbreviation: REMS, Risk Evaluation Mitigation Strategy.

*Calculated from the number of actual label changes.

The calculated 48% total label changes includes the 1 drug withdrawn from the market and those drugs with newly implemented REMS.
Percentage of safety-related label changes in the United States by data source - 2010
Public Data Extracts – What data are released?

- ~200,000 reports each quarter
- Over 50 data elements as reported from each case in the following area’s:

<table>
<thead>
<tr>
<th>Key Areas</th>
<th>Type of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>E.g. age, weight</td>
</tr>
<tr>
<td>Drug characteristics</td>
<td>E.g. drug name, dose, strength</td>
</tr>
<tr>
<td>Indication</td>
<td>MedDRA code of the indication for which the patient was treated</td>
</tr>
<tr>
<td>Outcome</td>
<td>E.g. hospitalization, death, life threatening</td>
</tr>
<tr>
<td>Reaction</td>
<td>MedDRA code for the drug reaction</td>
</tr>
<tr>
<td>Report Sources file</td>
<td>Health Professional, Study, Literature, Consumer etc.</td>
</tr>
<tr>
<td>Therapy Dates</td>
<td>E.g. start and end of drug therapy</td>
</tr>
</tbody>
</table>
Public Data Extract – What data are not released?

- **Personal Identifiable Information (PII)**
  - Data should not make it possible to identify individual patients

- **“Narrative”** - As it may contain, names, initials, phone number or other personal identifying information (PII)
  - “Narrative” is where the reporter describes the drug reaction in their own words

- **Patient’s address or the state**
  - We do release the country the event occurred or reported in

- **Death date**

- **Dates** like the onset date and the drug therapy dates are released but not dates like reaction dates which may, in some cases, imply a death date
Data Element - State

• 3 data elements related to state
  – **Reporter State**
    • Captured if reported by the reporter
  – **Sender Organization State** (Mfr.’s regulatory group send the AE)
    • Captured as part of the mandatory AE report
  – **Product Manufacturer State** (where product manufactured)
    • Only in reports submitted by industry
    – None of the state information is released as part of Public Data Extract
Compounded Product in FAERS

• Central Triage Unit identifies compounded products only from direct reports
  – “Compounded” is captured in the database
• Compounded products are coded to its active ingredient(s)
  – Discern from the report or by searching the web
  – No unique prefix or suffix identifying the ingredient as compounded
• “Compounded” identifier can be used as a search parameter
Questions?