Adverse Event Reports and Dietary Supplements

Supply Side East
April 28, 2010

Michael McGuffin
President, American Herbal Products Association
mmcguffin@ahpa.org
DS & OTC* Consumer Protection Act

- Sponsors: Senators Hatch (R-UT), Durbin (D-IL), Harkin (D-IA), Enzi (R-WY), and Kennedy (D-MA)
- Strongly supported by industry, as well as by consumer groups
- Effective December 22, 2007

* Dietary Supplement and Nonprescription Drug Consumer Protection Act
  (21 U.S.C. 379aa-1)
DS & OTC Consumer Protection Act

- Requires “domestic address” or “domestic phone number” on label (by 1/1/2010)
- “Responsible person” (usually company on label) must submit serious AERs (and “new medical info”) to FDA/CAERS w/in 15 days
- “Serious” defined ~as for drugs:
  Death; a life-threatening experience; inpatient hospitalization; significant or persistent disability; congenital anomaly or birth defect, OR requires, based on reasonable medical judgment, medical or surgical intervention to prevent above
DS & OTC Consumer Protection Act

RULE OF CONSTRUCTION.—The submission of any adverse event report in compliance with this section shall not be construed as an admission that the dietary supplement involved caused or contributed to the adverse event. 21 U.S.C. 379aa-1 (g)

“The committee emphasizes that adverse events are communications from consumers regarding events that may be associated with the use of a dietary supplement or nonprescription drug. The fact of a report of an adverse event is not determinative that the event occurred or that the event was caused by a consumer’s use of the product.” Senate Committee on Health, Education, Labor, and Pensions, Report 109-324
“A question has been raised about cases in which the responsible person may not agree with the reporter about the seriousness of an event. … If the manufacturer, packer, or distributor receives a report from a consumer who believes he or she has experienced a serious adverse event consistent with the definition above, it is the responsibility of the entity taking the report to forward that report to the FDA whether or not the reporter sought medical care or otherwise had proof of a serious adverse event” (emphasis added). Senate Committee on Health, Education, Labor, and Pensions, Report 109-324
DS & OTC Consumer Protection Act

Submission on MedWatch form 3500A; minimum data:

- an identifiable injured person (Section A)
- an identifiable initial reporter (E)
- identity and contact information for responsible person (G)
- a suspect product [dietary supplement or OTC drug] (C)
- a serious adverse event or fatal outcome (B)
- label (or copy) also required

Maintenance/inspection of all AERs also required/permissioned for 6 years
DS Adverse Event Reports

2008

Reporter to FDA (n=1013)

- Company: 627 (61%)
- Consumer / Friend / Health professional Family: 287 (28%)
- 99 (10%)
DS Adverse Event Reports

2008

Gender (where stated; n=1005)
DS Adverse Event Reports 2008

Age (where stated; n=768)

- < 10: 3%
- 10-19: 5%
- 20-29: 8%
- 30-39: 13%
- 40-49: 14%
- 50-59: 19%
- 60-69: 17%
- 70-79: 15%
- 80-89: 7%
- > 90: 0.8%

April 28, 2010
DS Adverse Event Reports 2008

Classifiable by Product Type (n = 825)

- Herbal: 249 (30%)
- Other primary ingredient: 391 (47%)
- Vitamin/mineral: 105 (13%)
- Combo: 80 (10%)

135 reports with multiple products; 65 reports ingredients unclear
Most common (single product = 890) reports:

- 103 (12%): Bayer One A Day (all formulas)
- 97 (11%): Total Body Formula
- 45 (5%): Centrum (all formulas)
- 34 (4%): Flintstones Vitamins (all formulas)
- 43 (5%): Mainstream calcium products
97 reports for Total Body Formula

- 26 AERs submitted from March 12-25; symptoms: significant hair loss, muscle cramps, diarrhea, joint pain and fatigue
- March 27: FDA issued consumer warning; excessive selenium / chromium
- 68 additional reports after warning
  [3 with date unclear]
- “Serious”?
Other FDA Actions

Hydroxycut recall

- May 1, 2009: FDA warns consumers to stop taking 14 Hydroxycut products
  
  *The FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to the FDA.*

  - AERs from 2002-2009
Other FDA Actions

- Body building products

  July 28, 2009: FDA warns consumers to stop taking “body building products represented as containing steroids or steroid-like substances.”

  The FDA has received five adverse event reports, including serious liver injury, in men taking products marketed as dietary supplements by American Cellular Laboratories including TREN-Xtreme and MASS Xtreme. Acute liver injury is generally known to be a possible side effect of using products that contain anabolic steroids. Some of the cases resulted in hospitalization, but there were no reports of death or acute liver failure.

  Warning letter issued re: these and 6 other products
DS AERs by “responsible person”
2008 / n=627

Outcomes Attributed to AE (MedWatch B2)
(n=627; Okay to check >1)

- Hospitalization: 229
- Required intervention: 16
- Disability: 8
- Life-threatening: 64
- Other serious +: 42
- Other serious ONLY: 312
- NONE Reported: 3
- Death: 8

April 28, 2010
DS AERs by “responsible person”
2008 / n=627

<table>
<thead>
<tr>
<th>21 U.S.C. 379aa-1 (a)(2)</th>
<th>MedWatch 3500A (B2)</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Death</td>
<td>8</td>
<td>1%</td>
</tr>
<tr>
<td>A life threatening experience</td>
<td>Life threatening</td>
<td>64</td>
<td>10%</td>
</tr>
<tr>
<td>Inpatient hospitalization</td>
<td>Hospitalization - initial or prolonged</td>
<td>229</td>
<td>37%</td>
</tr>
<tr>
<td>Persistent or significant disability or incapacity</td>
<td>Disability or permanent damage</td>
<td>8</td>
<td>1%</td>
</tr>
<tr>
<td>Congenital anomaly or birth defect</td>
<td>Congenital anomaly / birth defect</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Required intervention…</td>
<td>Required intervention…</td>
<td>23</td>
<td>4%</td>
</tr>
<tr>
<td>[no requirement to report other events]</td>
<td>Other serious (important medical events)</td>
<td>315</td>
<td>50%</td>
</tr>
</tbody>
</table>

April 28, 2010
“… the committee has limited the reporting requirement to the information FDA really needs: reports of death; a life-threatening experience; hospitalization; a persistent or significant disability or incapacity; a congenital anomaly or birth defect. In limiting the reporting system to serious events only, the committee recognizes that any broader reporting system could overburden manufacturers, consumers and the agency alike, generating information that may not be useful to the public health system at tremendous cost to all involved.” Senate Committee on Health, Education, Labor, and Pensions, Report 109-324
FDA Review of AERs

For all AERs received by FDA:

- Enter into the FDA CAERS database w/ MedDRA reporting terminology
- Review each by an FDA Medical Officer to determine the “strength of the evidence” of causality:
  - Uses WHO causality categories – certain; probable / likely; possible; unlikely; conditional / unclassified; and unassessable / unclassifiable.
  - Identifies confounding factors (underlying medical conditions; other products; travel; etc.)
- May review original language in submitted report, in addition to the MedDRA code language and other data entered into CAERS for that report.
FDA Review of AERs

For SAERs w/ certain, probable, or possible causality:

- May communicate with the report’s submitter to request additional information, or to request access to the subject of the event
- FDA considers that a “signal” has been generated:
  - By a group of reports if the number of similar reports is greater than established background norm within CAERS
  - By a cluster of similar SAERs associated a product (especially a newly introduced product) in a short time period
  - Unlikely by a single SAER for any given product
FDA Review of AERs

If a “signal” is identified, FDA will:

- Inspect marketer’s adverse event report files and collect more information on product (e.g., formulation; ingredients’ sources; etc.)
- Conducts / update literature searches for associated case reports (product or ingredients)
- Appoint FDA expert to make initial determination re: public health hazard
- Convene Health Hazard Evaluation Board (HHEB) of CFSAN Medical Officers and Chief Medical Officer; reviews all information and prepares report and conclusion
- Conduct risk-benefit analysis to meet the legal standard under the law; benefit needs to be “significant” (same standard that applies to evaluating drugs risks)
FDA Review of AERs

If FDA views the product as a significant or unreasonable risk:

- FDA contacts the product’s marketer and informs of conclusion; meeting is scheduled to provide company w/ opportunity to present additional information.
- If new information does not change FDA’s view the agency communicates its recommended action (e.g., recall).
Conclusions?

- “Responsible persons” are complying
  - Some over-reporting
  - Some under-reporting?
- Consumers / health providers may still report
- Majority of reports for combination and vitamin/mineral products
- Numbers small compared to drug AERs
- FDA is actively reviewing, and evidence of “signal” generation leads to agency action
THANK YOU!

Michael McGuffin
mmcguffin@ahpa.org

American Herbal Products Association

THE VOICE OF THE HERBAL PRODUCTS INDUSTRY