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Adverse Event Reports and Dietary Supplements

Supply Side East
April 28, 2010

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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)**

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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**

DS & OTC Consumer Protection Act

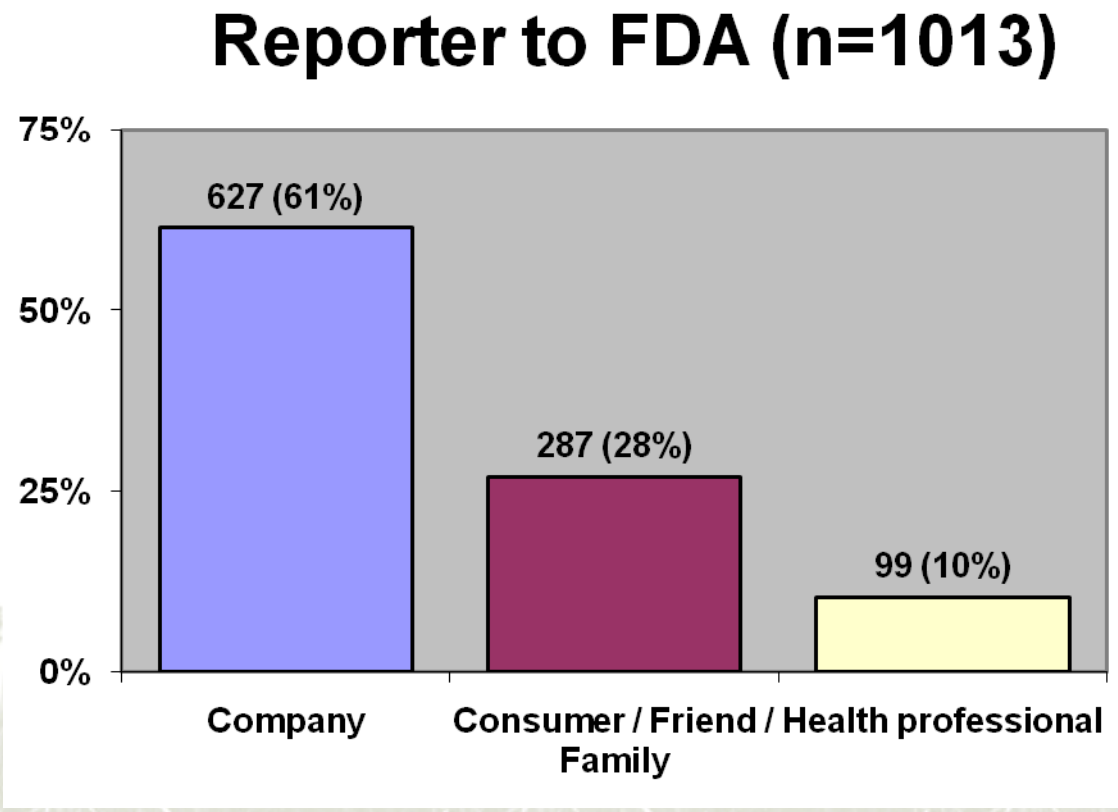
- **"A question has been raised about cases in which the responsible person may not agree with the reporter about the seriousness of an event. … If the manufacturer, packer, or distributor receives a report *from a consumer who believes he or she has experienced a serious adverse event consistent with 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/permitted for 6 years**

DS Adverse Event Reports

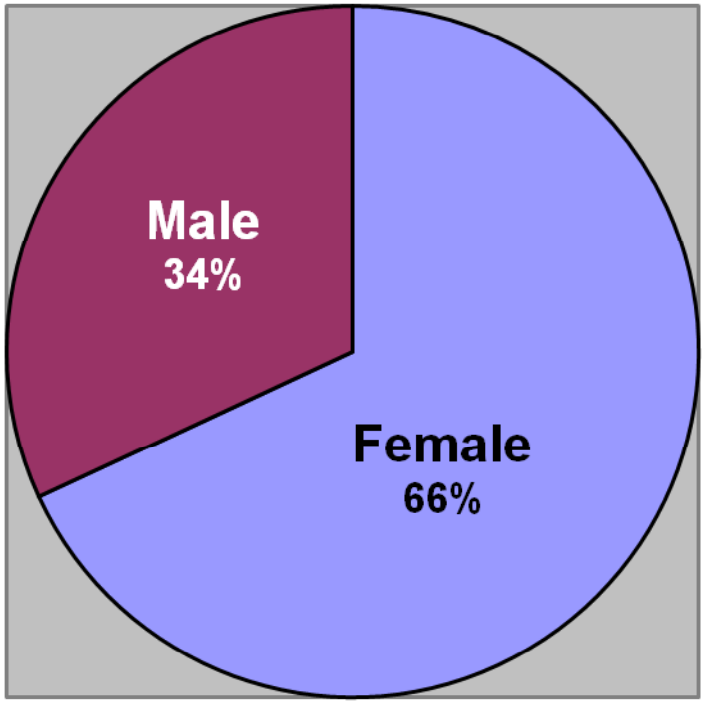
2008



DS Adverse Event Reports

2008

Gender (where stated; n=1005)



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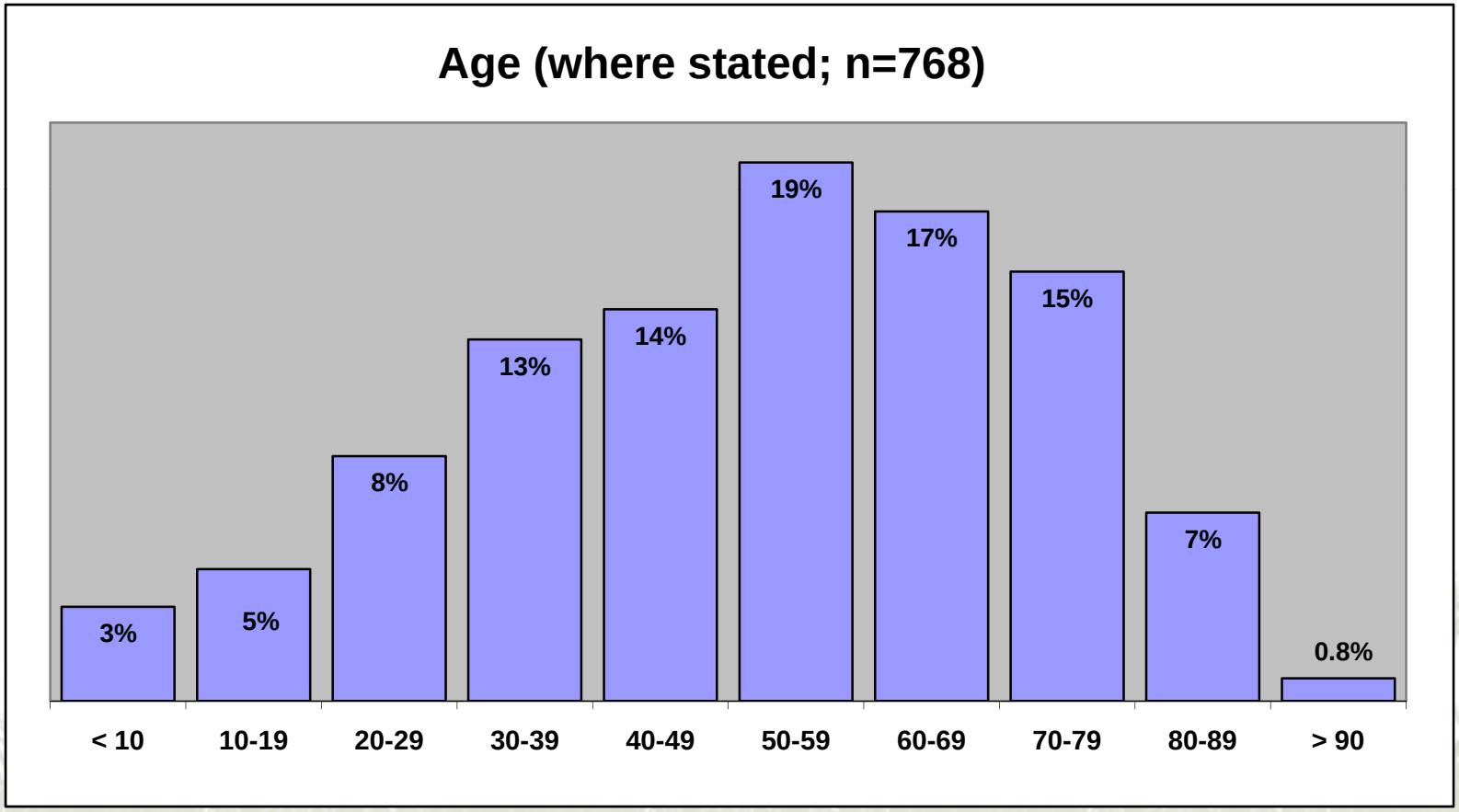
DS Adverse Event Reports

2008



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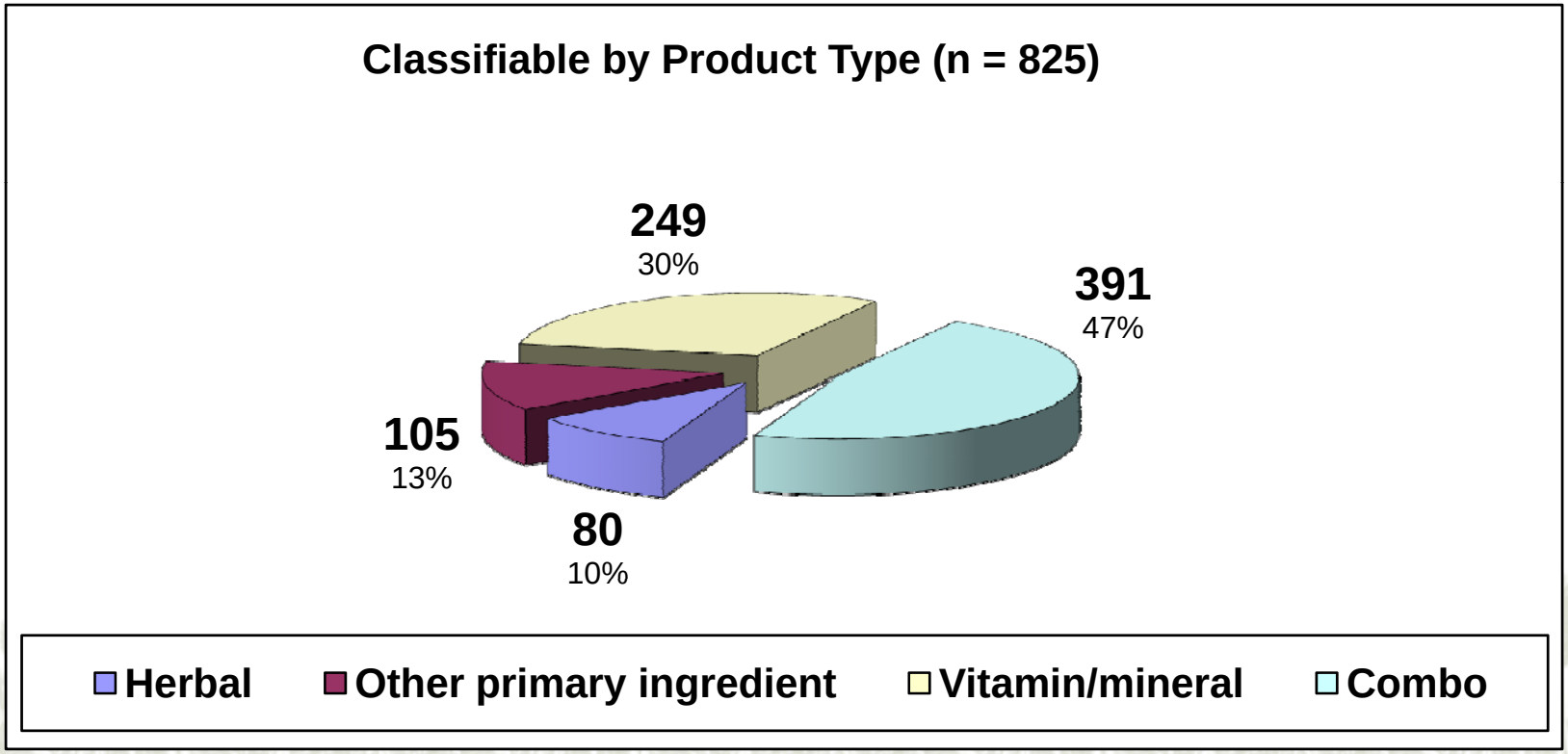
DS Adverse Event Reports

2008



135 reports w/ multiple products; 65 reports ingredients unclear

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DS Adverse Event Reports

2008

- **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**

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DS Adverse Event Reports

January – October 2008

- **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”?**

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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**

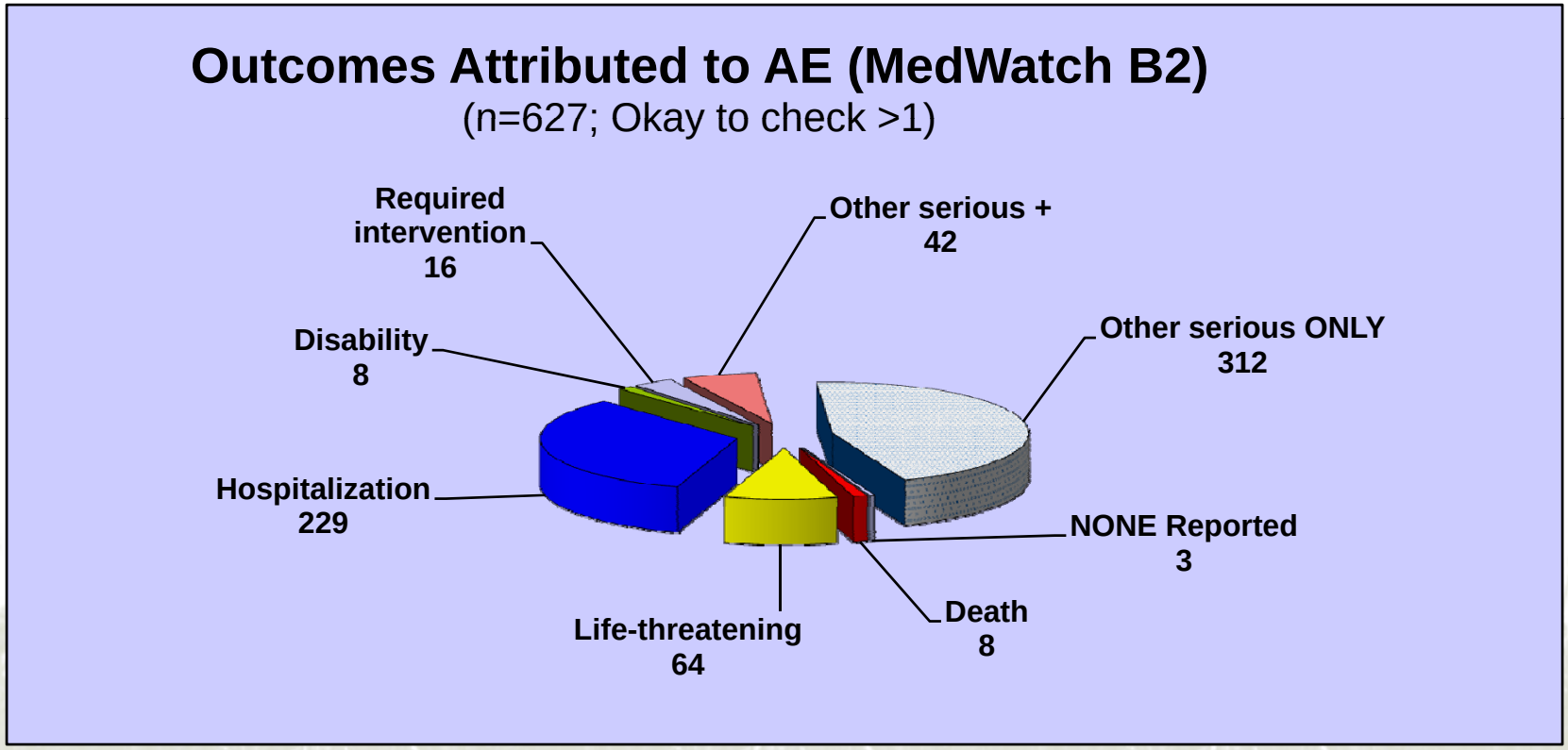
Other FDA Actions

- **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



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DS AERs by "responsible person"

2008 / n=627

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

DS & OTC Consumer Protection Act

- **"… 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

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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)

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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**

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THANK YOU!

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