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DIETARY SUPPLEMENT ADVERSE EVENT REPORTING: AVOIDING FDA AND HEALTH CANADA AE CITATIONS



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TOPICS FOR TODAY

- 1. FDA's new focus on enforcement and expectations for compliance
- 2. US vs. Canadian regulations: compare/contrast and methods of integration within a single PMS system
- 3. Review of recent FDA 483 warning letters involving AE violations
- 4. "Best Practices" regarding AE documentation, management, and regulatory reporting
- 5. "Best Practices" regarding evaluating and analysis of your own adverse event experience



SOME OF FDA'S EXPECTATIONS

- **x** Labels that meet 403(y)
- **×** SOP's for AERs and product complaints & related documents/records
- **×** Training of those that handle AERs
- **×** How does the firm obtain follow-up?
- * Has the firm ever sent SAERs to FDA? Have you ever received an AER?
- Does the firm monitor indirect sources of information on AERs? (e.g. social media, news)
- * How does the firm apply medical judgment for those reports they chose not to submit?
- **×** How are calls & mailed AERs routed if a 24-hr line isn't available?



POST-MARKET SURVEILLANCE/IN-MARKET SUPPORT VS. REGULATORY REPORTING

+ Post Market Surveillance

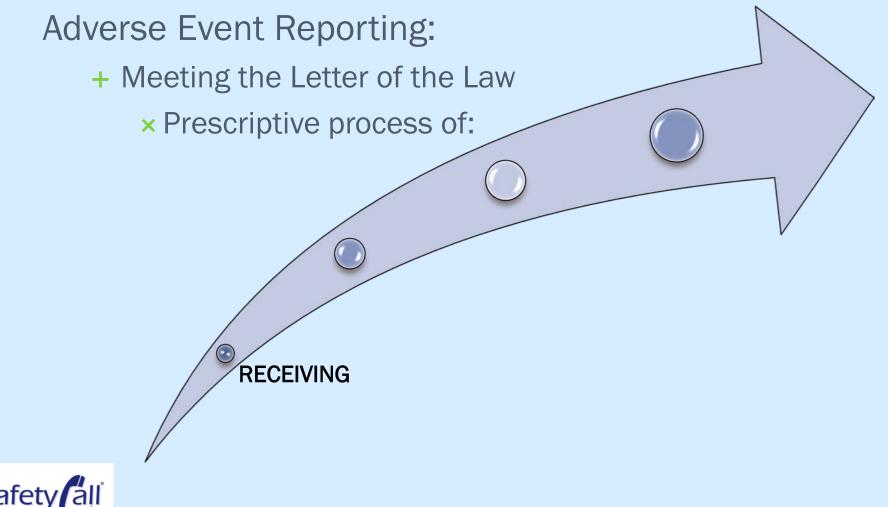
The processes whereby manufactures, regulators, health professionals, the public at large, and others monitor the performance and experience related to a given products life-cycle in the open market.

+ Regulatory Reporting

The prescriptive and *transparent* methods related to submitting AE reports as a surrogate measure of post-market surveillance effectiveness (no language in AE law requires analysis of findings)

















Dietary Supplement Mandatory AE Reporting

"DIETARY SUPPLEMENT AND NONPRESCRIPTION DRUG CONSUMER PROTECTION ACT"

- General Provisions and associated Implementation "Nuances" for US FDA regulations and Enforcement
 - + Who has to report?
 - + What has to be collected, recorded and archived?
 - + What has to be reported?
 - + When does it have to be reported?

+ What happens if you don't report it?



GENERAL PROVISIONS: WHO HAS TO REPORT

- **×** Reporting entities:
 - + The Manufacturer, Packer, Distributor whose name appears on the label
 - + Retailers may send AER's "upstream" to manufacturers or packers



GENERAL PROVISIONS: DATA COLLECTION VS. REPORTING

× Data Collection and maintenance of records:

+ "The responsible person shall maintain records related to each report of an adverse event..."

× AER's Defined:

"any health-related event associated with the use of a dietary supplement that is adverse"



COLLECTION PROCESS

- Minimum information for incident to be reportable:
 - + an identifiable patient;
 - + an identifiable reporter;
 - + a suspect product; and
 - + an adverse experience or fatal outcome suspected to be due to a product that has been used.



GENERAL PROVISIONS: WHAT TO REPORT

Any "serious adverse event" which is defined as an adverse health consequence that results in any of the following:

+ Death

- + A *life-threatening* experience
- + Inpatient hospitalization
- + A persistent or significant disability or incapacity; or
- + A congenital anomaly or birth defect; or
- + An incident that, "requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above"



GENERAL PROVISIONS: REPORTING PROCESS

- Each applicable event is reported on a standard FDA 3500a Form
 - + <u>http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm</u>
- The responsible person shall maintain records related to each report of an adverse event (serious or non-serious) received by the responsible person for a period of 6 years.
 - + Including raw data and any correspondence relating to the adverse event??
 - If a manufacturer fails to establish/maintain records, make reports, FDA may issue violations, levy fines and label a product as misbranded and/or unsafe.



U.S. Department of Health and Human Services Food and Drug Administration

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

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Form Approved: OMB No. 0910-0291, Expires: 10/31/08 See OMB statement on reverse.

Mfr Report # 734

UF/Importer Report #

				FDA USE ONLY
MEDWATCH FORM FDA 3500A (10/05)	(continued)	Dage 2	of 2	
F. FOR USE BY USER FA		-	H. DEVICE MANUFACTURERS O	NLY
Check One User Facility Impor User Facility or Importer Name/A	2. UF/Importer R		1. Type of Reportable Event Death Sorious Injury Malfunction Other:	2. If Follow-up, What Type? Correction Additional Information Response to FDA Request Device Evaluation
4. Contact Person	5. Phone Nu	mber	3. Device Evaluated by Manufacturer? Not Returned to Manufacturer Yes Evaluation Summary Attach	4. Device Manufacture Date (mm/yyy)
Importer Becamé Aware of Event (mm/dd/ywy)	Type of Report	8. Date of This Report (mm/dd/yyyy)	No (Attach page to explain why not) or provide code: . Evaluation Codes (Refer to coding manual)	5. Labeled for Single Use?
	roblem Codes (Rafar to codin	g manua) -	Mathod - Results - Conclusions -	
11. Report Sent to FDA? Yas No (mm/dd/yyy) 13. Report Sent to Manufacturer? Yas No (mm/dd/yyy) 14. Manufacturer Name/Address	12. Location Where Event O Hospital Hospital Outpatient Treatment Facility Other:	Outpatient Diagnostic Facility Ambulatory Surgical Facility	7. If Remedial Action Initiated, Check Type Recell Notification Repair Inspection Replace Patient Monitoring Relabeling Modification/ Adjustment Other	B. Usage of Device Initial Use of Device Reuse Unknown Statistics and to FDA under 1 USC 360i[f], list correction/ removal reporting number:
G. ALL MANUFACTURER 1. Contact Office - Name/Address (for Devices) Jane Doe Company X 1000 Langdon Rd Baltimore, MD 08223		2. Phone Number 201-111-2222 3. Report Source (Check all that apply) Foreign Study Literature Consumer Health Professional User Facility	10. Additional Manufacturer Narrative	and / or 11. Corrected Data
4. Date Received by Manufacturer (mm/dd/yyyy) 10/14/2004 6. If IND, Give Protocol # 7. Type of Report (Chock al that apply) 5-day 30-day 7. day Periodic 10-day X Initial X 15-day Follow-up # 0. Manufacturer Report Number 734	5. (A)NDA # IND # STN # PMA/ STN # Combination Product Pro-1938 Yas OTC Product Yas 8. Advorse Event Term(s)	Company Representative Distributor Other:		
The public reporting burden for this or minutes per response, including the sources, gathering and maintaining collaction of information. Sand comm this collection of information, including	time for reviewing instruction the data needed, and con	ns, searching existing data poleting and reviewing the	Department of Health and Human Services Food and Drug Administration - MccWatch 1003 New Hampshira Avonue Building 22, Mail Stop 4447 Silver Spring, MD 20083-0002 Please DO NOT RETURN this form to this add	OMB Statement: "An agency may not conduct or sponsor, and a precise is not required to respond to, a collection of information unless it deplays, a currently valid OMB control number."

GENERAL PROVISIONS: PENALTIES

× Penalties:

+ Clear deviations such as failure to submit AE reports, inaccurate information, incomplete disclosure of available information, lack of written procedures or failing to adhere to reporting requirements will result in manufacturer penalties.

The penalties can include, but are not limited to, product seizure, injunction, and/or civil/criminal penalties.







Natural Health Products AE Reporting



CANADA VIGILANCE PROGRAM

- Spontaneous Adverse Reaction Monitoring Program and Database, exists since 1965
- Reporting is *voluntary* for the general population, but is *mandatory* for Market Authorization Holders (MAH) as required by Canada's *Food and Drugs Act* and by the *Natural Health Products Regulations* (for NHPs)





ADVERSE REACTION REPORTING: DATA REQUIREMENTS

Minimum Data Requirements

x Both *voluntary* and *mandatory* AR reporting:

- 1. Identifiable patient
- 2. Description of the adverse reaction
- Suspected health product(s)
- 4. Identifiable reporter





AR REPORTING TO THE CANADA VIGILANCE PROGRAM

VOLUNTARY REPORTING

- Consumers and health professionals (medical doctors, naturopathic doctors, nurses, pharmacists) are encouraged to report ARs to health products, including NHPs
- **×** There are 3 ways to report an adverse reaction:
 - + Online
 - × <u>https://webprod4.hc-sc.gc.ca/medeffect-medeffet/index-eng.jsp</u>
 - + Completing a form (hard copy)
 - × Fax or mail
 - + Phone





AR REPORTING TO THE CANADA VIGILANCE PROGRAM

MANDATORY AR REPORTING BY NHP MAHS

Natural Health Products Regulations

Reaction Reporting (Section 24)

24.(1) A licensee shall provide the Minister with

- (a) a case report for each <u>serious</u> adverse reaction to the natural health product that occurs inside Canada, within **15 days** after the day on which the licensee becomes aware of the reaction; and
- (b) a case report for each <u>serious unexpected</u> adverse reaction to the natural health product that occurs inside or outside Canada, within 15 days after the day on which the licensee becomes aware of the reaction.





Natural Health Products Regulations

Definitions Related to AR Reporting

 "adverse reaction": a noxious and unintended response to a natural health product that occurs at any dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying an organic function





Natural Health Products Regulations

Definitions Related to AR Reporting (cont'd)

- "serious adverse reaction": a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death
- "serious unexpected adverse reaction": a serious adverse reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the natural health product





Natural Health Products Regulations

Reaction Reporting (Section 24)

- 24. (2) A licensee who sells a natural health product shall <u>annually</u> prepare and maintain a summary report that contains a concise and critical analysis of
 - (a) all adverse reactions to the natural health product that have occurred inside Canada; and
 - (b) all reactions for which a case report is required to be provided under subsection (1), that have occurred
 - (i) during the previous 12 months, and
 - (ii) at a dose used or tested for the diagnosis, treatment or prevention of a disease or for modifying organic functions in humans.





ANNUAL SUMMARY REPORTS: GENERAL PRINCIPLES

- **x** If a particular safety issue is detected,
 - + Health Canada may request the Annual Summary Report for a NHP
 - + Must be submitted within **30 calendar days**
- It is expected that MAH will notify Health Canada if a safety issue is detected during preparation of the Annual Summary Report
- ★ Records should be maintained on site (25 years), and made readily accessible
- MAH should be aware of any case reports that may not be directly reported to them:
 - + ARs published in the literature
 - + ARs submitted directly to Health Canada
 - MAH should request <u>line listings</u> from Health Canada or obtain via the Canada Vigilance Adverse Reaction Online Database
 - <u>http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php</u>





MANDATORY AR REPORTING - WHAT TO SUBMIT?

Types of Reactions	Expedited Case Report (15 days)	Annual Summary Report
Domestic Reactions (inside Canada)		
•Serious	Yes	Yes
•Serious unexpected	Yes	Yes
•Non-serious	No	Yes
•Non-serious unexpected	No	Yes
Foreign Reactions (outside Canada)		
•Serious	No	As needed
•Serious unexpected	Yes	Yes
•Non-serious	No	As needed
•Non-serious unexpected	No	As needed



AER REPORTING (US/CANADA) "TASK LIST TO ESTABLISH AER COMPLIANCE"

Establishing an in-house approach to post market surveillance:

- 1. Establish comprehensive SOP's for all aspects of your surveillance and reporting system, and train all company employees regarding the SOP's
- 2. Implement specific SOP's regarding Privacy (vs. HIPAA)
- 3. Design a database to manage collected reports
- Design an "intake system" (internal or external) including SOP's for triage of calls/incidents to appropriate and designated staff
- 5. Implement system to manage and document all incoming incidents from all methods of consumer communication (email, mail, phone calls, and social media)





AER REPORTING "TASK LIST TO ESTABLISH AER COMPLIANCE"

Establishing an in-house approach to post market surveillance:

- Insure that all "expedited reports" are filed within the 15day (Calendar/Business) reporting period
- 6. Data analysis and assessment for internal/external needs (mandatory in Canada, expected in the US)
 - Incident investigation and signal detection
 - × Trending/Benchmarking
 - Monitoring for Quality Issues and r/o of product incidents signaling manufacturing breaches
 - × Safety Profiling
 - Applying a DENOMINATOR perspective for incident normalization



AVOIDABLE CITATIONS

1

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U.S. Food and Drug Administration Protecting and Promoting *Your* Health

Home Inspections, Compliance, Enforcement, and Criminal Investigations Enforcement Actions Warning Letters

Inspections, Compliance, Enforcement, and Criminal Investigations

Mushroom Wisdom, Inc. 10/18/12

- 3. A qualified person from your firm did not investigate any product complaint that involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a risk of illness or injury, as required by 21 CFR 111.560(a)(2). For example:
- AER #1009 in October 2011, a consumer reported an allergic reaction to Super Cordyceps, Lot #090009. Your firm's report indicated that Lot #090009 was not from any of your batches within the past month and no further investigation was documented. However, upon review of your firm's released batches, Super Cordyceps, Lot #090009 was released on 10/25/2010 by your firm and has a expiration date of 09/2013.
- AER #1008- a customer reported on 06/01/2011 that her husband's blood pressure increased when taking Amyloban 3399. Your firm did not document any further investigation or findings.
- AER #1005- a customer reported on 07/12/2010 that her tongue was burned when she took Super Lion's Mane. Your firm did not document any further investigation or findings.



- 1. Developing a "sensitive system" and Normalized Incidence Rates
- 2. Determining acceptable ranges and actionable variations
- 3. Determining expected events based on toxicology and product design
- 4. Identifying predictable events and their expected incidence rates



- Incident integrity scoring (Consider that most consumer health care product events are spontaneously reported vs. clinical trial generated)
- 6. Identifying trends in low scoring unexpected events and considering potential relationship to product issues ie. "Sentinel Events" [Note: Dr. Fabricant comment re: hypothesis generation]
- 7. Identifying "Background Noise" or events occurring simultaneously but unrelated to product use



- 8. For suspected "Sentinel" events or for deviations in expected incidence rates do individual incidents represent:
 - a) Quality Control issues/Contamination
 - i. Before leaving the plant
 - ii. After leaving the plant
 - Direct but predictable or previously recognized adverse effects based on inherent toxicology/pharmacology of the product or an ingredient
 - I. Dose dependent
 - II. Dose independent (idiosyncratic)



- c) Direct but previously unrecognized adverse effect of the product or an ingredient:
 - i. Idiosyncratic, unpredictable in occurrence but predictably occurring at a low incidence rate within the population
 - ii. Long Term effects secondary to chronicity of use (eg. New soy research)
- d) Interaction related event involving use of the product and:
 - i. Other Drug, Supplement, or ingredient within the same product
 - ii. Disease
 - iii. Food
 - iv. Environment
 - v. Biologic (gene expression)
 - vi. OTHER CONSUMER PRODUCT CONCOMMITANTLY BEING USED
 - vii. Old Botanical or new use botanical
- e) Counterfeit Product



- 9. Are reported effects in any given category preventable?
- 10. Can reported effects in any given category be prevented, managed and/or mitigated through:
 - a. Disclosure
 - b. Education
 - c. Reformulation
 - d. New manufacturing process (change in solvents)
 - e. New product design (multi-ingredient review)
 - f. Dosage adjustment
 - g. Market withdrawal or recall



"BEST PRACTICE" COMPANIES

- + Examples of "Best Practice" approaches to Post Market Surveillance:
 - × Insure Accessibility
 - × Assign professional staff
 - × Engage outside credible 3rd party oversight of findings
 - × Establish a dedicated database vs. AE data in multiple databases
 - Establish a feedback loop for GMP analytical review of suspect products identified in AE experience deviations
 - Conduct a trending analysis with both their domestic and foreign experience

× ACT ON RESULTS



SUPPLEMENT SAFETY SURVEILLANCE

CONNECTING THE DOTS:

"Did use of the product cause, or contribute to, the reported or observed adverse effects"

INCLUDES EFFORTS OF MANUFACTURERS, REGULATORS, HEALTH PROFESSIONALS, RESEARCHERS, INSURANCE CARRIERS, PRODUCT LIABILITY EXPERTS



WEIGHT OF EVIDENCE MODELING

- Natural Product Health Hazard Evaluation (HHE)
 Process used to identify "unsafe" products
 - + Typically no single "silver bullet" of regulatory information
 - Utilizes multiple systems of surveillance and assessment individualized for each issue
 - + Combines evidence based science with market data
 - Maximally engages the manufacturer to participate in the assessment through sharing of corporate AE surveillance findings and science information
 - × Confirming safety known's
 - × GMP and quality control consideration
 - Consumer experiences including sensitive surveillance monitoring from spontaneous reports





THANK YOU!

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