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

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

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SOME OF FDA'S EXPECTATIONS

- 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)

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ADVERSE EVENT REPORTING VS. POST-MARKET SURVEILLANCE

Adverse Event Reporting:

- + Meeting the Letter of the Law
  - × Prescriptive process of:

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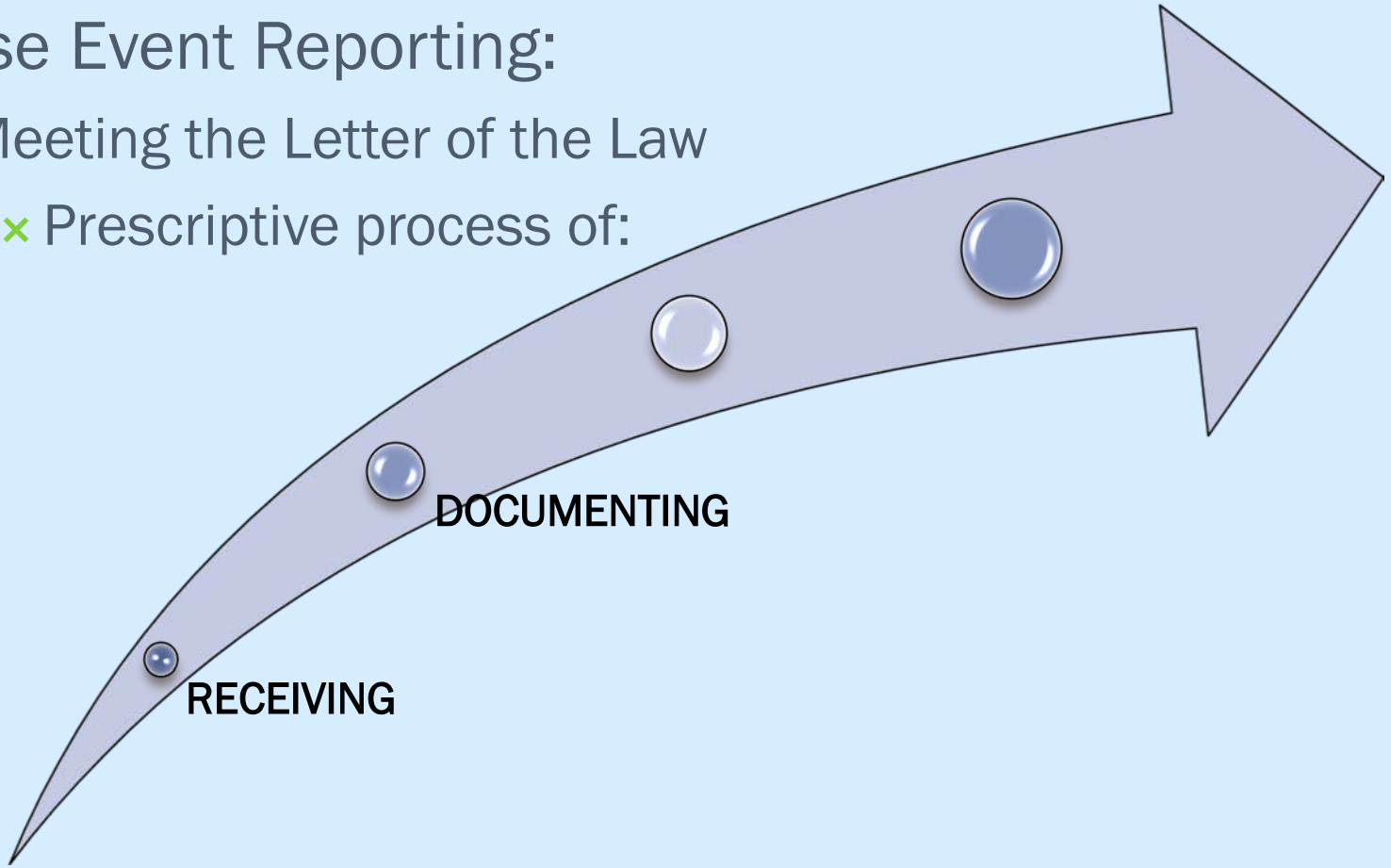

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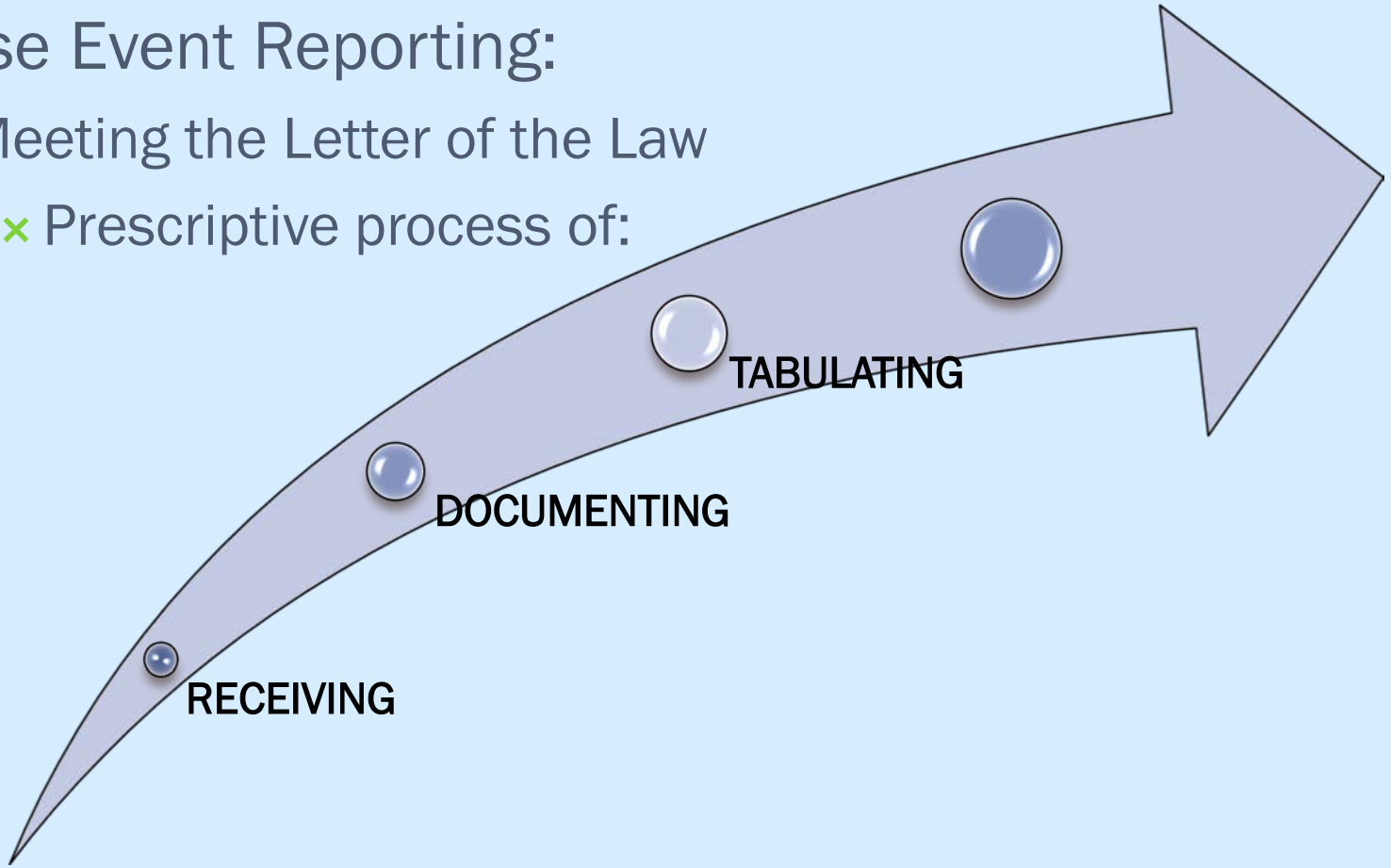

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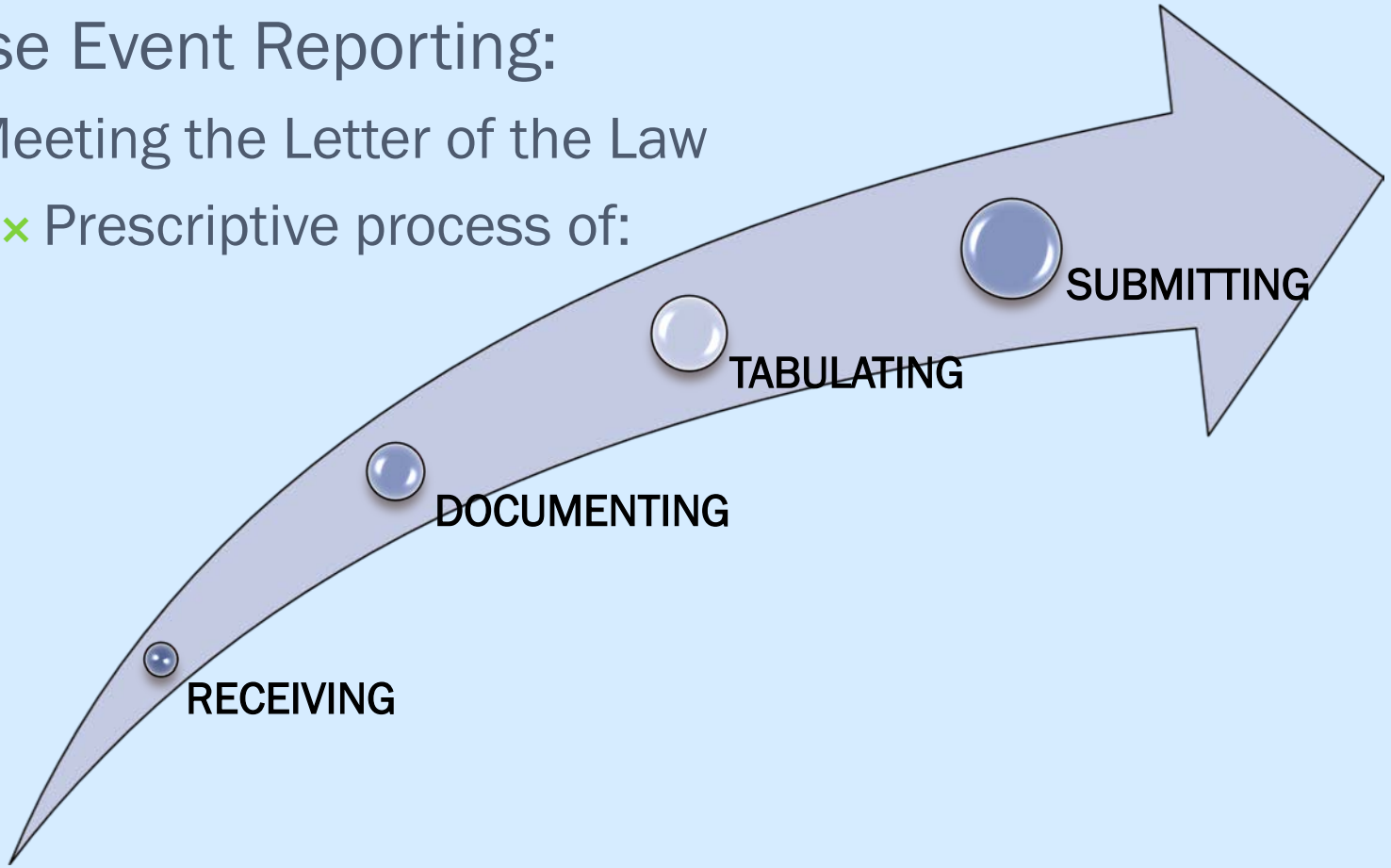

UNITED STATES FOOD AND DRUG ADMINISTRATION

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?

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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

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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”

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GENERAL PROVISIONS: REPORTING PROCESS

- Each applicable event is reported on a standard FDA 3500a Form
  - http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- 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.

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

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

MEDWATCH

FORM FDA 3500A (10/05)

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

Mfr Report # 734

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier: DS (In confidence)
2. Age at Time of Event: 23 Year(s) or Date of Birth:
3. Sex: ☐ Female ☒ Male
4. Weight: UNK lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- ☐ Death: (mm/dd/yyyy)
- ☐ Disability or Permanent Damage
- ☐ Life-threatening
- ☐ Congenital Anomaly/Birth Defect
- ☒ Hospitalization - initial or prolonged
- ☒ Other Serious (Important Medical Events)
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy): 10/14/2004
4. Date of This Report (mm/dd/yyyy): 10/14/2004

5. Describe Event or Problem

Patient reports that he recently started to use the product last night for first time. He slept badly, but took another dose this am with 2 cups of coffee. He has taken a total of 8 capsules over the past 24 hours. He had recently worked out at his local Gym. When he returned home, approximately 2 hrs later, he reports that he developed 'heart palpitations', dizziness, and nausea. Sx have been persisting x 30 min. He was instructed to go to the ER immediately.

Follow-up on Oct 15, 2004
Spoke with physician caring for this patient. Patient presented to their hospital ER last evening with complaints of dizziness, nausea, and vomiting. His body temperature was 102.1, and his physical exam suggested dehydration. His BP was 95/50 on presentation, and his HR was 144. EKG showed frequent runs of supraventricular tachycardia. Patient was immediately treated with IV fluids. His SVTs were treated with three bolus doses of adenosine. SVTs resolved within 1 hours of presentation. The patient was admitted to their coronary care unit for overnight observation, and discharged this morning following the complete resolution of all of his symptoms.

It was determined that the patient was taking this supplement with another thermogenic weightloss supplement resulting in his intake of 2000 mg caffeine over a 12 hour period prior to his presentation. The patient had also been working out heavily in a gym that was not air conditioned.

6. Relevant Tests/Laboratory Data, Including Dates

EKG showed supraventricular tachycardia

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

healthy

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labelar)
- #1 Guarana Lean
- #2 Body Thermofuel

2. Dose, Frequency & Route Used
- #1 2 Capsules orally X1
- #2 6 tablets over 12 hour period

3. Therapy Dates (If unknown, give duration from/to (or best estimate))
- #1 10/13/2004 to 10/14/2004
- #2 10/13/2007 to 10/14/2007

4. Diagnosis for Use (Indication)
- #1 NA
- #2 NA

5. Event Abated After Use Stopped or Dose Reduced?
- #1 ☒ Yes ☐ No ☐ Doesn't Apply
- #2 ☒ Yes ☐ No ☐ Doesn't Apply

6. Lot #
- #1 2TAB6
- #2 UNK

7. Exp. Date
- #1 11/2007
- #2 UNK

8. Event Reappeared After Reintroduction?
- #1 ☐ Yes ☐ No ☒ Doesn't Apply
- #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# or Unique ID: 41000-08896

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

NI

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (mm/dd/yyyy) / Serial # / Other #
5. Operator of Device: ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) ☐ Yes ☐ No ☐ Returned to Manufacturer on: (mm/dd/yyyy)
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. INITIAL REPORTER

1. Name and Address

Dr. Roger Moore

General Hospital
Minneapolis, MN 55118

Phone #: 612-200-2000

2. Health Professional? ☐ Yes ☒ No
3. Occupation: Physician
4. Initial Reporter Also Sent Report to FDA ☐ Yes ☒ No ☐ Unk.

MEDWATCH

FORM FDA 3500A (10/05) *(continued)* Page 2 of 2

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One: ☐ User Facility ☐ Importer
2. UF/Importer Report Number:
3. User Facility or Importer Name/Address:
4. Contact Person:
5. Phone Number:
6. Date User Facility or Importer Became Aware of Event *(mm/dd/yyyy)*:
7. Type of Report: ☐ Initial ☐ Follow-up #
8. Date of This Report *(mm/dd/yyyy)*:
9. Approximate Age of Device:
10. Event Problem Codes *(Refer to coding manual)*: Patient Code - - ; Device Code - -
11. Report Sent to FDA? ☐ Yes *(mm/dd/yyyy)* ☐ No
12. Location Where Event Occurred: ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: *(Specify)*
13. Report Sent to Manufacturer? ☐ Yes *(mm/dd/yyyy)* ☐ No
14. Manufacturer Name/Address:

G. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site 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 ☐ Company Representative ☐ Distributor ☐ Other:
4. Date Received by Manufacturer *(mm/dd/yyyy)*: 10/14/2004
5. (A)NDA # ; IND # ; STN # ; PMA/510(k) # ; Combination Product ☐ Yes ; Pre-1938 ☐ Yes ; OTC Product ☐ Yes
6. If IND, Give Protocol #:
7. Type of Report *(Check all that apply)*: ☐ 5-day ☐ 30-day ☐ 7-day ☐ Periodic ☐ 10-day ☒ Initial ☒ 15-day ☐ Follow-up #
8. Adverse Event Term(s):
9. Manufacturer Report Number: 734

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event: ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other:
2. If Follow-up, What Type? ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer? ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code:
4. Device Manufacture Date *(mm/yyyy)*:
5. Labeled for Single Use? ☐ Yes ☐ No
6. Evaluation Codes *(Refer to coding manual)*: Method - - - ; Results - - - ; Conclusions - - -
7. If Remedial Action Initiated, Check Type: ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment ☐ Other:
8. Usage of Device: ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

Please DO NOT RETURN this form to this address.

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.

HEALTH CANADA

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

- Both ***voluntary*** and ***mandatory*** AR reporting:
  1. Identifiable patient
  2. Description of the adverse reaction
  3. 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
    - https://webprod4.hc-sc.gc.ca/medeffect-medeffet/index-eng.jsp
  - 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 serious 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 serious unexpected 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.

MANDATORY AR REPORTING BY NHP MAHS

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

MANDATORY AR REPORTING BY NHP MAHS

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

MANDATORY AR REPORTING BY NHP MAHS

Natural Health Products Regulations

Reaction Reporting (Section 24)

24. **(2) A licensee who sells a natural health product shall annually 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

- 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 line listings from Health Canada or obtain via the Canada Vigilance Adverse Reaction Online Database
    - http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php

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
4. 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*)

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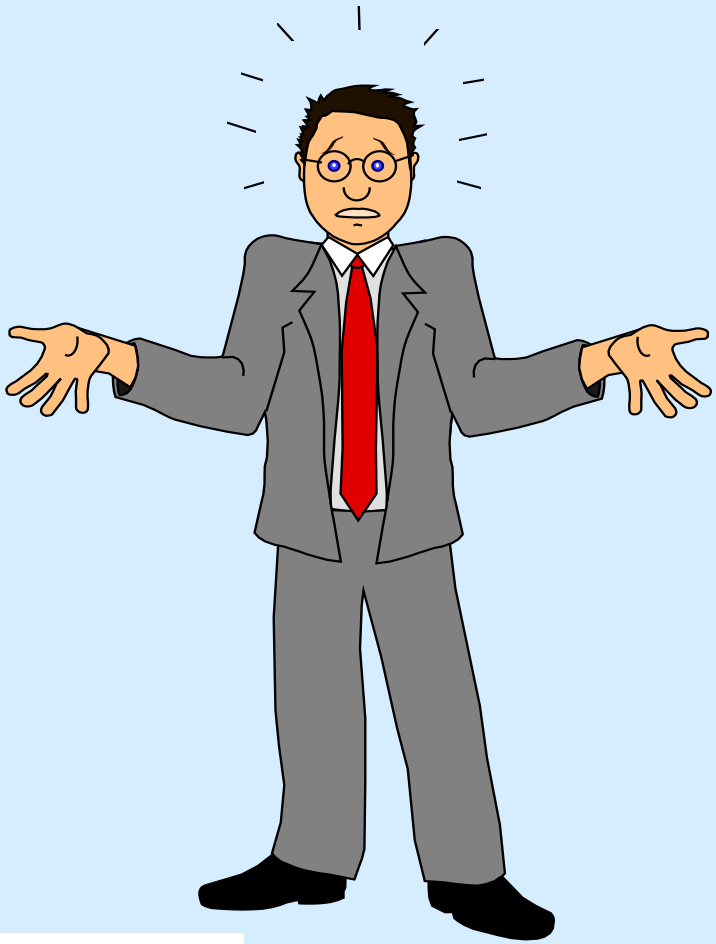
AER REPORTING
"TASK LIST TO ESTABLISH AER COMPLIANCE"

Establishing an in-house approach to post market surveillance:

5. 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



But I reported all those allegations of my product causing arms to spontaneously fall off!!!

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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.

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CORPORATE POST-MARKET SURVEILLANCE
TOP 10 "BEST PRACTICE" SAFETY STEPS

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

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CORPORATE POST-MARKET SURVEILLANCE TOP 10 "BEST PRACTICE" SAFETY STEPS

5. 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

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CORPORATE POST-MARKET SURVEILLANCE TOP 10 "BEST PRACTICE" SAFETY STEPS

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
    b) 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)

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CORPORATE POST-MARKET SURVEILLANCE TOP 10 "BEST PRACTICE" SAFETY STEPS

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

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CORPORATE POST-MARKET SURVEILLANCE
TOP 10 "BEST PRACTICE" SAFETY STEPS

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

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"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

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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***

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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

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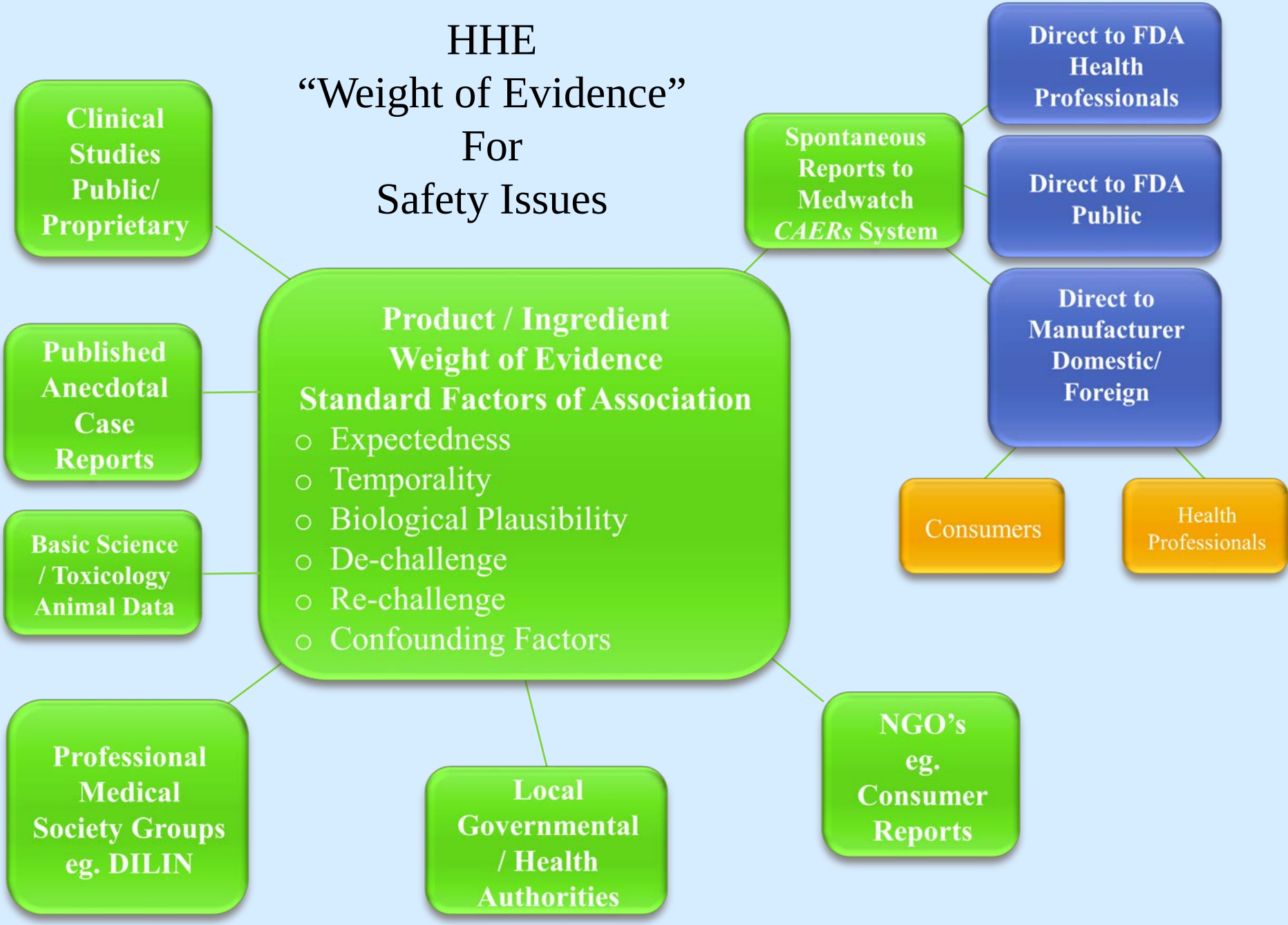
HHE
"Weight of Evidence"
For
Safety Issues



THANK YOU!

RKINGSTON@SAFETYCALL.COM