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Enforcement, Litigation, and Compliance Conference

December 7-8, 2016
Washington, DC

Preparing for and Responding to FDA Enforcement Actions – Advance Topics: Food and Dietary Supplements

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Issues: Food Inspections, Recalls and Enforcement Actions

FDLI Enforcement, Litigation and Compliance Conference

December 7, 2016

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Inspections – Risk of Recall

- Evidence to be considered by FDA in determining whether to seek a voluntary recall or issue a recall order
  - Observations during inspections
  - Review of FSMA-required records
  - Results from sample analyses (product and environmental)
  - Epidemiological data
  - Reportable Food Registry data
  - Consumer and trade complaints

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Inspections – Risk of Recall

- Noncompliance may indicate that food is adulterated under
  - § 402(a)(3) - manufactured in way that is unfit for food
  - § 402(a)(4) - prepared, packed or held under insanitary conditions whereby it may have been contaminated with filth or rendered injurious to health

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Inspections – Risk of Recall

- FSMA - broader records access during inspections
  - If FDA believes there is a “reasonable probability” of serious adverse health consequences or death to humans or animals (SAHCODHA hazard) from consumption of a food
  - Also, access to records of related products if FDA has a reasonable belief that related products are likely to be affected in a similar manner

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Challenges – Pathogen Testing

- Pathogen detected in random product sample
  - Positive test result for product with multiple ingredients; no positives when test ingredients
  - Evaluate need for recall if product is past shelf life
  - Difficulty confirming sampling/testing details
  - Concerns re methodology used
  - Risk of false positive
  - If positive test result for a commodity ingredient, it may be difficulty to confirm supplier

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Challenges – Illness Outbreaks

- Preliminary epidemiological evidence links foodborne illness outbreak to product
  - Suspected food source may change during investigation
  - May not be a positive in product or facility
  - May not be a validated methodology at the time a recall decision must be made
- At what point is there sufficient information to justify a recall?

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Challenges – Illness Outbreaks

- Pulsed-field gel electrophoresis (PFGE)
  - Compares fragments of DNA; may not show significant differences among strains; no food source found in ~1/3 of outbreaks (using PFGE)
- Whole genome sequencing (WGS)
  - Examines complete genome
  - Investigations are more accurate/rapid; cases can be solved with data from as few as 3 illnesses, down from typically10-12 illnesses before the use of WGS

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Challenges – WGS

- Industry questions:
  - "Closely related genetically" and "likely source" -- adequate legally re recalls, criminal actions, product liability?
  - Re WGS, is the SNPs (single-nucleotide polymorphisms) method used by FDA equivalent to the wgMLST (whole-genome multilocus sequence typing) method used by CDC?
  - Do the agencies recognized any limitations of WGS?
  - Are the agencies developing a compliance policy guide re use of WGS in regulatory actions?

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Strict Criminal Liability

- “Responsible Corporate Officer Doctrine (Park Doctrine)
- Misdemeanor conviction, under public welfare laws based on:
  - Position in company and relationship to violation
  - Authority to prevent/correct violation
  - No knowledge/participation necessary
- Statutory penalties – per misdemeanor count
  - Imprisonment for up to 1 year or fine of up to $1,000, or both
  - Max fine of $100,000 for individuals, if no death results

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Strict Criminal Liability -- Examples

- Mr. Park (1975) -- insanitary conditions; conviction
  - $250 fine ($50 per count)
- Jenson brothers (2014) -- *Lm* outbreak; pled guilty
  - 6 months “home” detention; 5 years' probation; $150,000 restitution; 100 hours community service
- DeCoster brothers (2015) -- *Salmonella* outbreak; pled guilty
  - 3 months in prison; 1 year of supervised release; $100,000 fine

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Appeal in DeCoster

- Appealed prison sentences to 8th Circuit Court of Appeals – unconstitutional
  - Due Process Clause – stipulation (no proof the DeCosters knew eggs causing the outbreak were adulterated)
  - 8th Amendment (sentences not proportional to the crimes)
  - Procedurally unreasonable (trial court relied on erroneous facts)
  - Substantively unreasonable (prior regulatory violations -- not shown to involve the DeCosters and unrelated to the outbreak)

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Appeal in DeCoster

- Court of Appeals – affirmed prison sentences (7/2016)
  - Trial court: the DeCosters “created a work environment where employees not only felt comfortable disregarding regulations and bribing USDA officials, but may have felt pressure to do so”
  - Appellate court: “the district court properly considered relevant past conduct and imposed substantively reasonable sentences ”
- DeCosters requested rehearing; denied (9/2016)
- DeCosters plan to seek review by U.S. Supreme Court

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Dietary Supplements: Enforcement Focus Areas

December 2016

Allison Fulton
Sidley Austin, LLP

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Supplements – Focus Areas

1. Unsafe Supplements – A Continued Federal Focus
2. Label Accuracy – A State Focus
3. cGMP – 2016 Warning Letter Trends
4. Dietary Supplement Serious Adverse Events – Pointers

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Unsafe Supplements – A Continued Federal Focus

- DOJ / FDA "nationwide sweep" in November 2015
  - Undeclared ingredients
  - Bogus claims
  - Often in combination with cGMP violations or reported adverse events
- "The criminal charges against USPlabs should serve as notice to industry that if products are a threat to public health, the FDA will exercise its full authority under the law to protect Americans and bring justice."

  -- Howard Sklamberg, FDA Deputy Commissioner, Global Regulatory Operations and Policy

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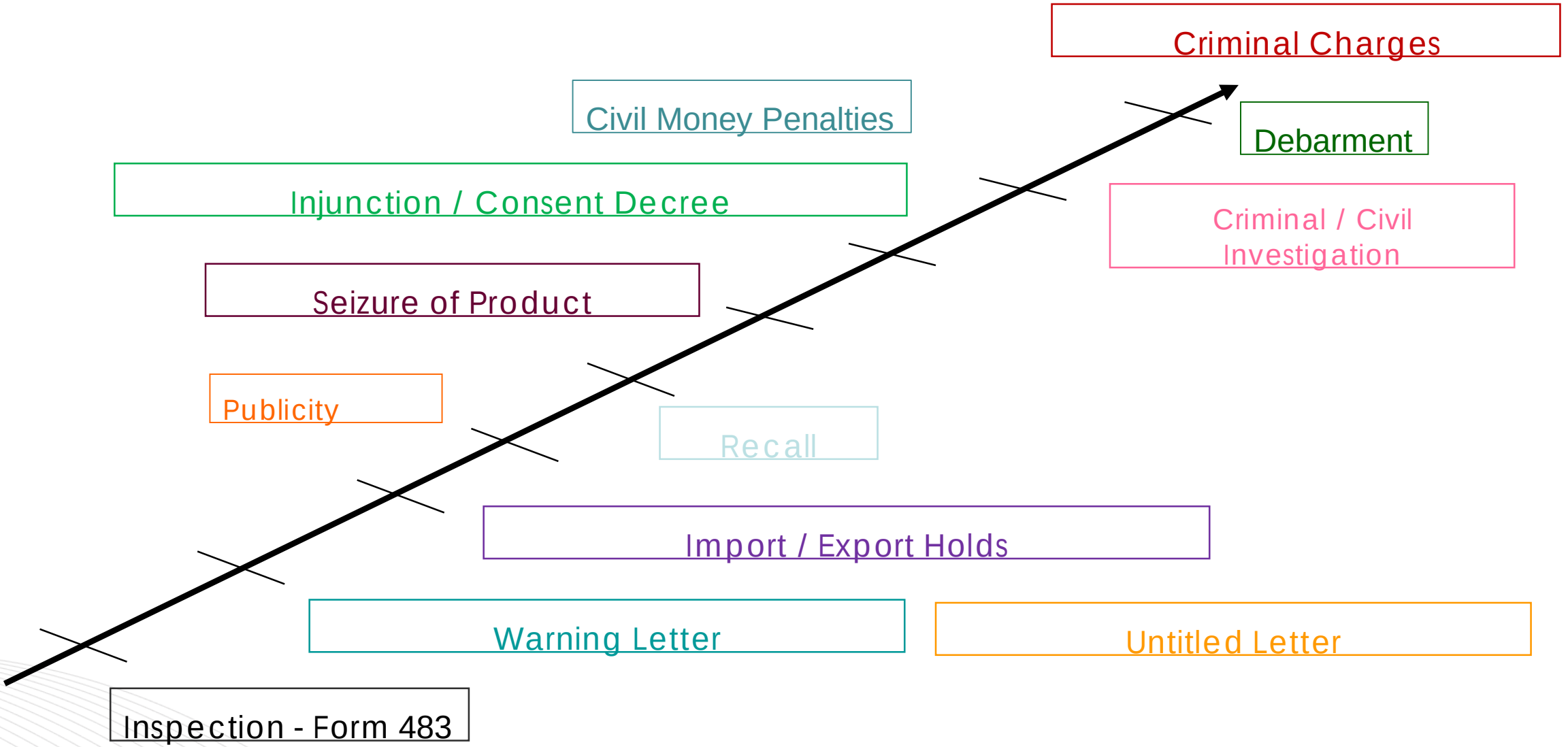
FDA Enforcement Tools



Label Accuracy – A State Focus

- States continue to express interest in supplements, post NY state Attorney General (AG) initiative in 2015
- Subpoenas issued by state AGs may focus on:

1. Accuracy: Does the product have what the label promises?
   - ➢Nutrient
   - ➢Amount of nutrient
2. Stability: Does the product meet its labeled claims throughout the shelf life?
   - ➢What does the testing data show?

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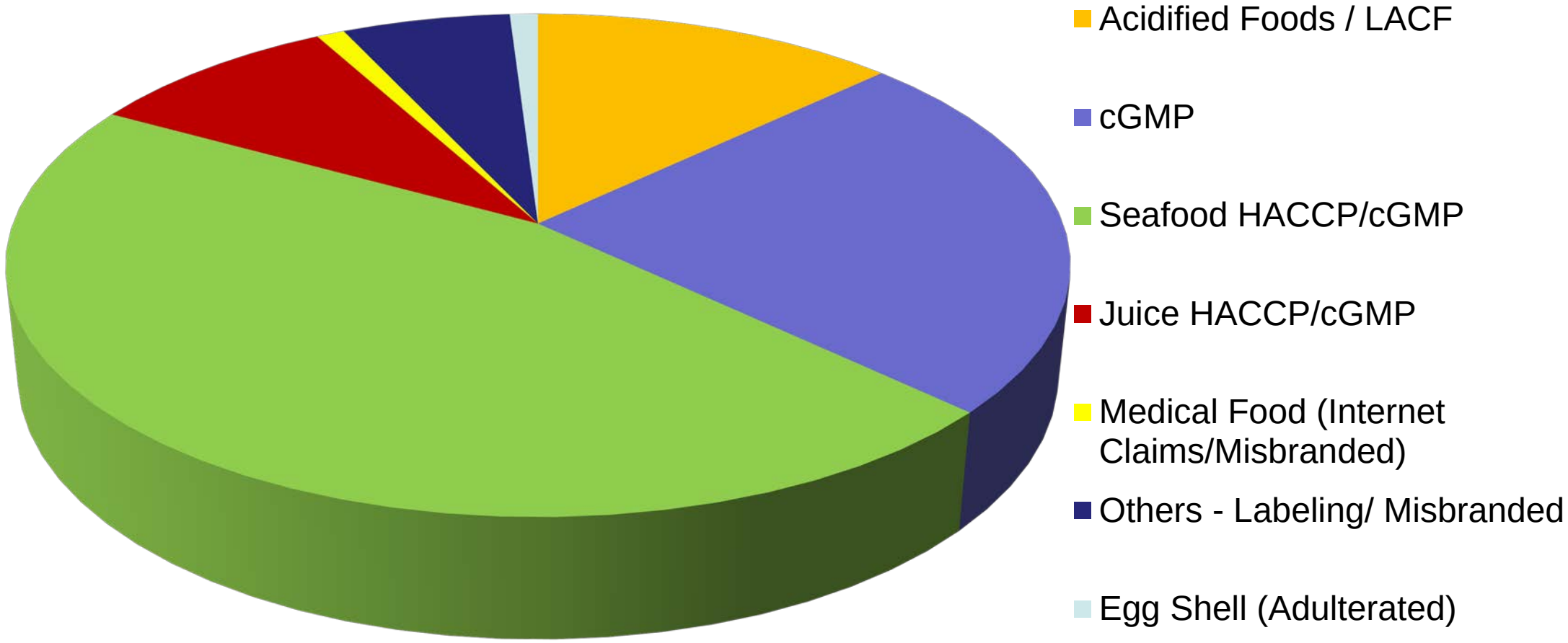
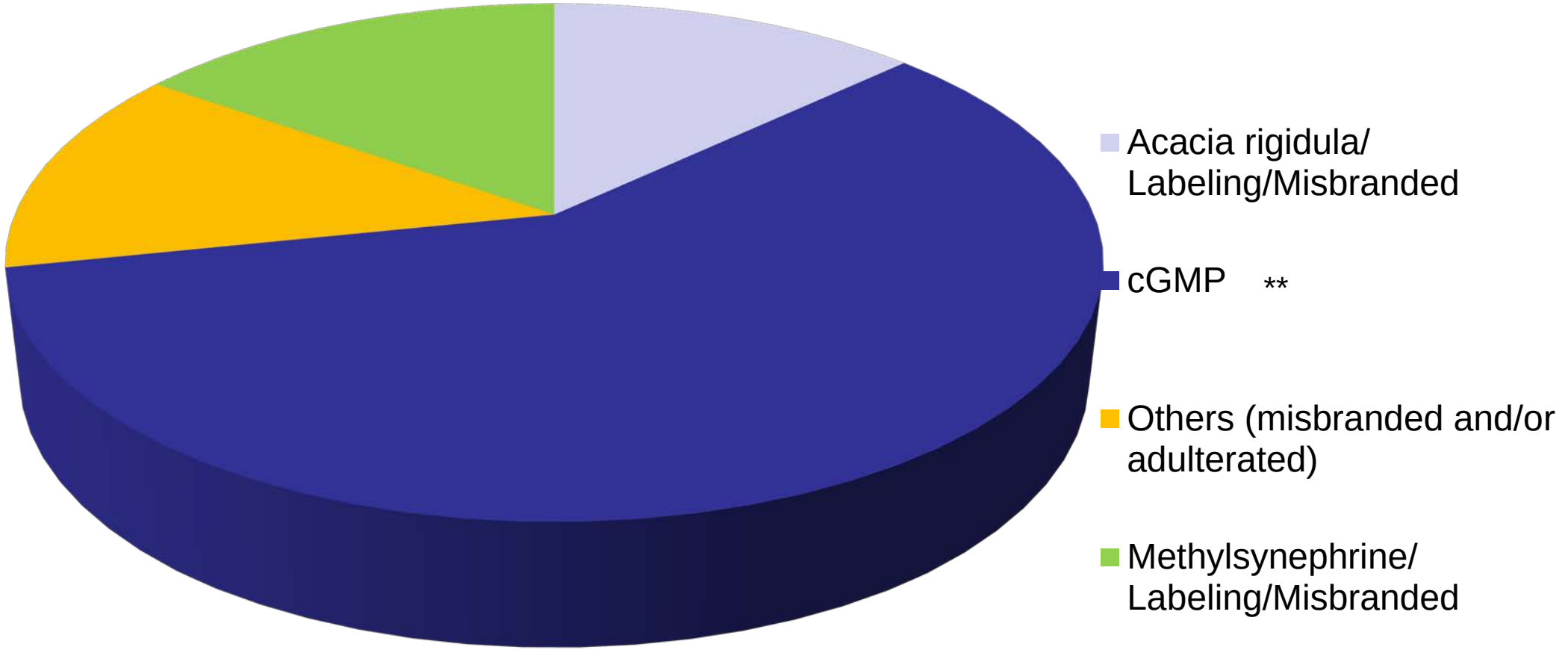
2016 Warning Letter Trends - Food



* Source: Warning Letters made publically available by MediRegs (05Dec2016)

2016 Warning Letter Trends – Dietary Supplements

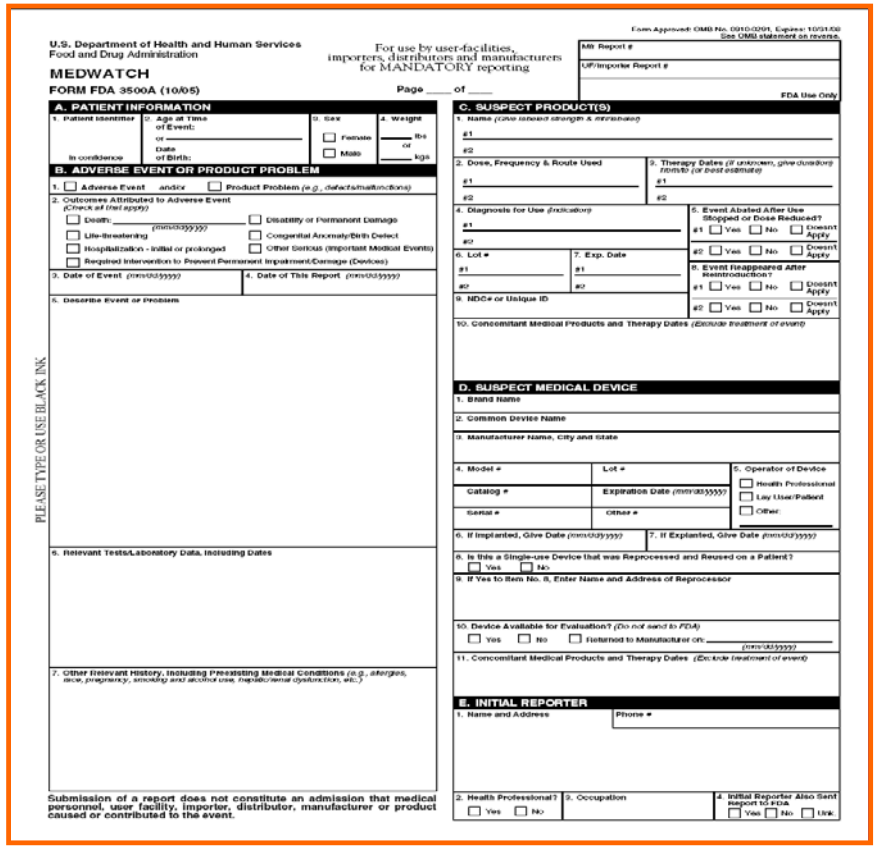


* Source: Warning Letters made publically available by MediRegs (05Dec2016)

** Also cite unapproved drug claims / misbranding violations

Serious Adverse Event Reporting – Pointers

1. Causality is <u>not</u> the threshold for reporting
2. Causality determination also not required for internal quality records
3. Obtain required information on the <u>first</u> call
4. Make reasonable efforts to follow up with the reporter, and document those efforts
5. Always consider product liability claims
6. Audit to ensure right decision, consistent decisions



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

Page ___ of ___

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

MW Report #

UF/Importer Report #

FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier — In confidence

2. Age at Time of Event: or Date of Birth:

3. Sex — Female / Male

4. Weight — lbs or kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defect/malfunction)

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)

4. Date of This Report (mm/dd/yyyy)

5. Describe Event or Problem

6. Relevant Tests/Laboratory Data, Including Dates

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

C. SUSPECT PRODUCT(S)

1. Name (Give strength & manufacturer)
#1
#2

2. Dose, Frequency & Route Used

3. Therapy Dates (if unknown, give duration) (mm/dd or best estimate)

4. Diagnosis for Use (Indication)

5. Event Abated After Use Stopped or Dose Reduced?

6. Lot #

7. Exp. Date

8. Event Reappeared After Reintroduction?

9. NDC# or Unique ID

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

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

Phone #

2. Health Professional? Yes / No

3. Occupation

4. Initial Reporter Also Sent Report to FDA Yes / No / Unk

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.

PLEASE TYPE OR USE BLACK INK

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Challenges And Opportunities When Communicating With The Food And Drug Administration About Food Inspections

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Presented to:
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Washington, D.C.

Proactive Steps That Will Prepare You For An FDA Inspection

- Look to your left, look to your right
  - e.g., what FDA has done to your food competitors and what are the hot issues in your industry (or sub-industry)
    - review Warning Letters
- Find out about the people with whom you might be dealing with at FDA, such as the inspector conducting the inspection
  - ask your colleagues, network
- Conduct mock audits and internal review and, where appropriate, enlist outside assistance
- Train employees to manage inspections

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Proactive Steps That Will Prepare You For An FDA Inspection *(cont'd.)*

- Have an open door policy where employees can share concerns
- Know your rights, as well as FDA's inspectional authority
- Make sure policies and quality systems are manageable (but remember cooperation is always better with a regulatory body)
  - ➢ sufficiently detailed to provide guidance and ensure compliance

    but

  - ➢ not too rigid that you're destined to fail and where you leave no room for common-sense flexibility
  - ➢ use FDA definitions – don't be too creative

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Proactive Steps That Will Prepare You For An FDA Inspection *(cont'd.)*

- There should be a Standard Operating Procedure (SOP) or an inspection plan that describes who is the point person at the company to deal with FDA and the do's and don'ts
- The company's liaison must know where certain documents are located, because not knowing gives a poor impression and causes delays (and could be perceived as denying access to FDA, a violation of law)
  - ➢ be knowledgeable about company employees' responsibilities and corporate policies and control the investigator's access

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Demonstrate That Compliance Is A Priority

- Try to get on your company's agenda for the next major meeting at your company to discuss compliance issues
  - shows other groups at the company that senior management cares and believes compliance is a priority
  - shows that compliance (and non-compliance) affects the whole company and each group is not an island
  - no silos – you're part of a team

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(Some) Common Mistakes Companies Make With FDA

- Misconception that FDA will act as a consultant and always act objectively
- Misconception that FDA will give smaller companies a regulatory "pass," because of size or limited resources
- Misconception that FDA will meet its deadlines or communicate effectively
- Misconception that FDA will admit it is wrong
- Not knowing your rights

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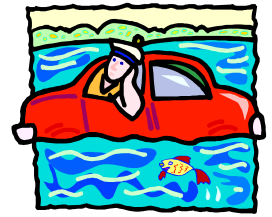
Response Game Plan



- Form a Response Team
- Review FDA enforcement correspondence for accuracy, clarity, completeness, and foundation
- Submit a timely written response (within 15 business days)
- In cases where you disagree with the investigator, provide a complete explanation in support of the company's position

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Response Game Plan *(cont'd.)*

- Seek clarification and understand the issues
- Respond quickly to agency requests, state company position clearly, and implement corrective action
  - ➢ have a neutral advisor review and offer suggestions for next steps and resolution
- Check ego at door – arrogance is a major turnoff and is counterproductive
- Issue information to important constituents as soon as possible

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Response Game Plan *(cont'd.)*

- Document decisions, but keep it simple
- Give yourself credit for what you have done
  - e.g., training, documentation
- But don't give yourself too much credit
  - no one likes a braggart and the enforcement action indicates your company is not perfect
- See the big picture – read between the lines

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Response Game Plan *(cont'd.)*

- Have proactive timelines for corrective action that are credible and achievable and keep commitments to FDA
  - don't promise what you can't deliver
  - if you promise something, you'd better deliver
  - give yourself some flexibility with standard operating procedures and deadlines, so long as compliance is met
  - haste can make waste

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Response Game Plan *(cont'd.)*

- Consider requesting a meeting with FDA District Office
- Determine whether it is useful to bring the matter to FDA headquarters
- Prepare for follow-up inspection, especially if a Warning Letter has been received
- Convey commitment to compliance
  - ➢ consider what resources and commitments will be involved if you had to sign a consent decree

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How to Enhance Your Relationship With FDA

- Put yourself in FDA's position
- Listen carefully to FDA, even if it sounds like the question asked or information requested seems odd
- Have a plan of action and backup plan
- Do not play hardball, but do not be too soft – cooperation and appreciation of FDA's job tends to work better
- Ask questions to understand the "big picture"
- Be responsive/flexible

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How to Enhance Your Relationship With FDA *(cont'd.)*

- Follow through on commitments
- Create a high level of confidence in the company's abilities
  - ➢ credibility is key
  - ➢ check your assumption and know your weaknesses
    - ❑ be a healthy skeptic and avoid the Beautiful Baby Syndrome

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For more information, please contact:

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