REGULATORY TRAINING DIRECT

5.01. U.S. Dietary Supplements

Rend Al-Mondhiry, Partner
Amin Talati Wasserman LLP

AMIN | TALATI WASSERMAN

Agenda

Ingredient Requirements

- Defining “Dietary Supplement”
- Allowable Dosage Forms
- Drug Exclusionary Clause
- New vs. Old Dietary Ingredients

Labeling

- Required Labeling Elements
- Additional Labeling Considerations
- Misbranding
- California’s Proposition 65

Agenda

Quality & Safety

- Adulteration Standard
- Good Manufacturing Practices (GMP) Requirements
  - Inspections & Enforcement
- Adverse Event Reporting
- Food Safety Modernization Act (FSMA)
  - FSMA Rules
  - FSMA Enforcement Tools

Defining “Dietary Supplement”

Dietary supplements are regulated as **food** under the Federal Food, Drug & Cosmetic Act (FD&C Act)

Adverse Event Reporting

cGMPs

Claims

No pre-market approval

Defining “Dietary Supplement”

The Dietary Supplement Health and Education Act of 1994 (“DSHEA”) amended the FD&C Act to define “dietary supplement” as a product intended to supplement the diet that contains one, or any combination, of the following substances:

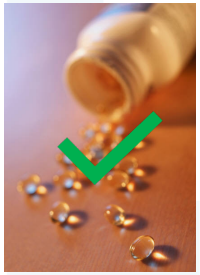
- **(A) vitamin;**
- **(B) mineral;**
- **(C) herb or other botanical;**
- **(D) amino acid;**
- **(E) dietary substance for use by man to supplement the diet by increasing the total dietary intake; or,**
- **(F) concentrate, metabolite, constituent, or extract of any of these ingredients**

Dosage Forms

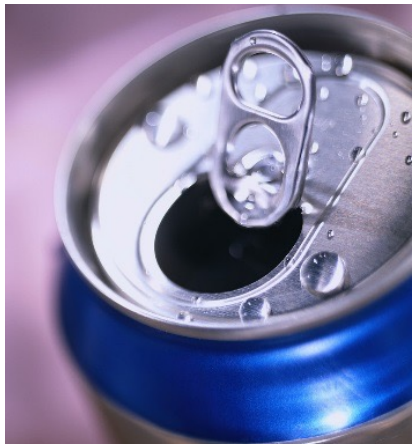
Must be intended for ***ingestion***

- Cannot be injected, inhaled, absorbed through mucosa, administered sublingually, or transdermal

May be in many forms such as tablets, capsules, soft gels, gel caps, liquids, or powders



Dosage Forms



Cannot be represented as a conventional food/beverage, or as a meal replacement

- *FDA Guidance for Industry: Distinguishing Liquid Dietary Supplements from Beverages* (2014)
- Intended to help companies determine whether a product in liquid form is properly classified as a dietary supplement or beverage
- Describes the factors that distinguish liquid dietary supplements from conventional foods
  - Product name, packaging, serving size, directions for use, marketing practices, composition, other representations, e.g., statements in filings with SEC or USPTO

Drug Exclusionary Clause

- Under the FD&C Act, articles that have been approved as drug, or authorized for investigation as a new drug for which “substantial clinical investigations” have been instituted and have been made public, are excluded from the definition of dietary supplement
- Exceptions:
  - The article was marketed as a dietary supplement or conventional food before the new drug investigations were authorized, or
  - The Secretary of HHS, in the Secretary’s discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter
- Examples include:
  - Cannabidiol (CBD)
  - N-Acetyl Cysteine (NAC)
  - Nicotinamide mononucleotide (NMN)

Drug Exclusionary Clause

Warning Letters to N-acetyl cysteine (NAC) supplement marketers

- Marketed to treat/prevent hangover, but also excluded from being a supplement because it was approved as an (inhaled) drug in 1964
- Two Citizens Petitions filed in 2021 asking FDA to find that NAC is not excluded from the definition of "dietary supplement" under the FD&C Act

"…we are considering initiating rulemaking to provide by regulation that NAC is not excluded from the definition of dietary supplement. If, among other considerations, the FDA does not identify safety-related concerns as we continue our review of the available data and information, we are likely to propose a rule providing that NAC is not excluded from the definition of dietary supplement.."

New vs. Old Dietary Ingredients

- DSHEA made clear that supplement ingredients could not be regulated as food additives
- Instead, two categories of ingredients:
  - **"Old" or grandfathered ingredients marketed *in the U.S. before* October 15, 1994 are considered safe for continued consumer use**
    - FDA has considered the development of an old dietary ingredient list.
  - **"New" dietary ingredients are those marketed *after* October 15, 1994**
- All non-dietary ingredients (e.g., excipients) must be Generally Recognized as Safe (GRAS) for their intended use, or approved food additives

New vs. Old Dietary Ingredients

New ingredients must be notified to FDA with an explanation that the ingredient "is reasonably expected to be safe, " or are adulterated

Exception for ingredients present in the food supply, such as GRAS ingredients and approved food additives, that are not "chemically altered" (i.e., unchanged from food)

***Not** restricted to the U.S. food supply*

Notification must be provided to FDA at least 75 days before going to market

Different safety standard vs. food additives; **not an "approval"**

FDA will "acknowledge" (i.e., not object to) the NDI notification, or may object on the basis that the NDI is not a dietary ingredient/supplement, safety or identity of the ingredient is inadequate, or the notification is incomplete

New vs. Old Dietary Ingredients

Acknowledgement letters without objections (AKL)

Not dietary ingredient/dietary supplement (NDL)

Inadequate safety/identity (IAL)

Incomplete (ICL)

New vs. Old Dietary Ingredients

Recent Updates to the List of NDINs

For your convenience, the following are entries that have recently been updated.

New Dietary Ingredient Notification #	Name of New Dietary Ingredient	Firm	Date of Submission	Date of FDA's Response
1254	ProGo®	Hofseth BioCare ASA	5/25/2022	7/27/2022
1255	TEES-10® Ligularia stenocephala extract powder	Famenity Co. Ltd.	7/13/2022	9/19/2022
1256	Greenyn Insumate® powder	Greenyn Biotechnology Co., Ltd.	7/21/2022	9/21/2022
1257	Crocin Rich®	Quality Phytochemicals LLC	7/21/2022	9/23/2022
1258	Lactobacillus paracasei subsp. paracasei HY2782; Lacticaseibacillus paracasei subsp. paracasei HY2782; or Lactobacillus casei HY2782	hy Co., Ltd.	7/22/2022	9/27/2022
1259	β-Nicotinamide Mononucleotide (NMN)	Inner Mongolia Kingdomway Pharmaceutical Limited	7/28/2022	10/11/2022
1260	Buckwheat Husk Extract	TCI Co., Ltd	9/2/2022	11/9/2022
1261	Weissella confusa WIKIM51 (Wilac D001)	Pharmsville Co., Ltd.	11/18/2022	12/19/2022
1262	EuBone®	Chenland Nutritionals, Inc	9/30/2022	12/1/2022
1263	Alomac - powdered Aloe macroclada gel	JWJames Consulting	10/19/2022	12/30/2022
1264	NPI-001, a dried kratom leaf powder	Johnson Foods LLC	10/21/2022	1/4/2023

New vs. Old Dietary Ingredients

- Enforcement of NDI requirements through FDA Warning Letters
- *"No information demonstrating that higenamine and hordenine were lawfully marketed as dietary ingredients in the United States before October 15, 1994, nor is there information demonstrating that higenamine and hordenine have been present in the food supply as articles used for human food in a form in which the food has not been chemically altered."*
  - Therefore, subject to the premarket NDI notification requirement
- *"FDA has not received any NDI notifications pertaining to the use of higenamine or hordenine have in dietary supplements. Products for which the manufacturer or distributor is required to submit a new dietary ingredient notification, but for which the required notification has not been submitted, are adulterated."*
  - Subject to injunction and seizure

Labeling


to U.S. Pharmacopeia
ndards. Laboratory
Supplement
Serving Size 1 Tablet
Each Tablet Contains
Vitamin A 3500 I.U.
as Beta-Carotene
C 90 mg
400 I.U.

Required Labeling Elements

1. Statement of identity
2. Net quantity of contents
3. Nutrition labeling
4. Ingredient list
5. Company Information

21 CFR 101.36

Required Labeling Elements

Required Label Statements	Location
Statement of Identity	PDP
Net Quantity of Contents	PDP
Nutrition Label	IP
Ingredients/Other Ingredients List	IP
Allergen Statement (if required)	IP
Company Information	IP
Required Warning Statements (if applicable)	IP
FDA Disclaimer (if structure/ function claims made)	Same panel as claim
"Material" Warnings	IP if room; anywhere if not

Required Labeling Elements

1. Statement of Identity

- Must be appropriately descriptive and include the word “supplement”
  - E.g., “Dietary Supplement” or “Calcium Supplement,” but not “Sleep Supplement”
- Must be one of the prominent features on the Principal Display Panel

2. Net Quantity of Contents

- Accurate statement of the amount of the dietary supplement in the container or package
  - Must be expressed in either weight, measure, numerical count (e.g., “30 capsules”), or a combination of numerical count and weight or measure

Required Labeling Elements

3. Nutrition Labeling

- Supplement Facts Panel
  - Different variations based on intended use, (e.g. products for children and adults), multi-pack products
  - Alternate formats for small and intermediate size packages
- Key differences from Nutrition Facts:
  - May list Proprietary Blends
  - Must list dietary ingredients without RDIs or DRVs
  - May list source of the ingredient
  - Must include part of plant from which an ingredient is derived
  - Cannot list “zero” amounts of nutrients

Supplement Facts

Serving Size 1 Capsule
Servings Per Container 100

Amount Per Capsule	% Daily Value
Calories 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 765 mcg	85%
Vitamin D 21 mcg	105%
Omega-3 fatty acids 0.5 g	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

Required Labeling Elements

4. Ingredient List

- Must be preceded by the word “Ingredients” except that “Other Ingredients” must be used when some ingredients (i.e., as sources) are identified with the nutrition label
  - “Other ingredients” typically includes non-dietary ingredients, such as binders, colors, excipients, fillers, flavors, and sweeteners
- Listed in order of predominance by weight

Supplement Facts

Serving Size 1 Capsule
Servings Per Container 100

Amount Per Capsule	% Daily Value
Calories 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 765 mcg	85%
Vitamin D 21 mcg	105%
Omega-3 fatty acids 0.5 g	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

5. Company Information

- Name and place of business of the manufacturer, packer, or distributor
- Must list the street address if it is not listed in a current city directory or telephone book (or online directory), city, state, and zip code
  - Country of origin labeling requirements also apply

Additional Labeling Considerations

- FDA Disclaimer
  - If a structure/function claim, e.g., “Supports joint health,” is made on the label or in labeling, it must be accompanied by a disclaimer informing consumers that FDA has not evaluated the claims and that the product is not intended to diagnose, treat, cure, or prevent any disease because only a drug can legally make such a claim
  - 21 CFR 101.93

***These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Additional Labeling Considerations

Country of Origin Labeling

- Regulated by U.S. Customs & Border Protection (CBP
- If required, statement of the country of origin must appear in close proximity to the company information
- FTC regulates “Made in U.S.A.” claims, which are *voluntary*

Organic Claims

- Regulated by the U.S. Department of Agriculture (USDA)
- Claims must be used in strict compliance with National Organic Program regulations

Additional Labeling Considerations

Expiration Dating

- Not required, but if provided must be supported by valid data to demonstrate it is not false or misleading

Warning Statements

- Mandatory warning for certain iron-containing supplements regarding accidental overdose by children under 6
  - Warnings for certain protein, psyllium products
- Otherwise, no specific warnings required but general misbranding provisions apply
  - Must reveal material facts relevant to the consequences of using a supplement

Food Allergen Labeling and Consumer Protection Act

- Allergens must be declared on the label directly under the ingredient statement if the product contains one of the **nine** major food allergens:
  - Milk, eggs, fish (must specify species), crustacean shellfish (must specify species), tree nuts (must specify type), peanuts, wheat, soybeans, sesame
- E.g.,: Contains Milk; Contains Tree Nuts (Coconut)

Additional Labeling Considerations

Voluntary Best Practices

- General dietary supplement warning:
  - "Consult your physician before use if you are pregnant, nursing, have a medical condition, or are taking any medication. Keep out of reach of children."
- Trade association voluntary labeling guidelines
  - Warnings related to caffeine, melatonin, kava

AHPA
AMERICAN HERBAL PRODUCTS ASSOCIATION

CRN The Science Behind the Supplements
CELEBRATING 50 YEARS 1973-2023

Misbranding

DSHEA provides that a dietary supplement is misbranded if the label or labeling of the supplement fails to:

- List the name of each ingredient of the supplement and the quantity of each such ingredient, or with respect to a proprietary blend of such ingredients, the total quantity of all ingredients in the blend
- Identify the product by using the term “dietary supplement,” which term may be modified with the name of such an ingredient
- Identify any part of the plant from which an herb or botanical ingredient is derived

A supplement is also misbranded if it:

- Is covered by the specifications of an official compendium, is represented as conforming to the specifications of an official compendium; and fails to so conform; or
- **Is not** covered by the specifications of an official compendium and fails to have the identity and strength that the supplement is represented to have, or fails to meet the quality (including tablet or capsule disintegration), purity, or compositional specifications, based on validated assay or other appropriate methods, that the supplement is represented to meet

California's Proposition 65

- The Safe Drinking Water and Toxic Enforcement Act, known as Proposition 65
  - Ballot initiative in 1986; requires a "person doing business" in the state to provide a "clear and reasonable warning" for exposures to certain chemicals
  - Applies to dietary supplements and other foods

WARNING: Consuming this product can expose you to chemicals including [name of one or more chemicals], which is [are] known to the State of California to cause cancer and birth defects or other reproductive harm. For more information go to www.P65Warnings.ca.gov/food.

⚠ **WARNING**: Cancer – www.P65Warnings.ca.gov.

⚠ **WARNING** Cancer and Reproductive Harm – www.P65Warnings.ca.gov.

California's Proposition 65

State agency (OEHHA) maintains a list of chemicals known by the state to cause cancer or reproductive toxicity

- **Over 900 chemicals** currently listed
- Naturally occurring and synthetics, e.g., lead, certain pesticides

Enforced by the California AG and plaintiffs' bar

- No demonstration of actual harm required; burden entirely on the defendant

Quality & Safety

Adulteration Standard

DSHEA provides that a dietary supplement or dietary ingredient is adulterated (unsafe) if it:

- "Presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling…or under ordinary conditions of use"
- Contains an NDI "for which there is inadequate information to provide assurance that it does not present a significant or unreasonable risk of illness or injury"
- Poses "an imminent hazard to public health or safety"

Food adulteration provisions also apply to dietary supplements:

- Prohibition against poisonous or deleterious substances
- Prohibition against contamination with insanitary or injurious substances
- Prohibition against unapproved color additives
- Functional components (e.g., excipients) must also comply with these provisions

FDA has the burden of proof to show that a dietary supplement is adulterated

Adulteration Standard

Ephedra

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
P04-106
November 23, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Acts to Remove Ephedra-Containing Dietary Supplements From Market

The Food and Drug Administration today intensified its efforts to protect consumers against harmful products and their sometimes fatal side effects by taking enforcement action against dietary supplements with ephedrine alkaloids marketed as a treatment for serious diseases and conditions.

"We are once again sending a message that HHS and the FDA will not tolerate the marketing of dietary supplements that are more likely to harm health than help it," said HHS Secretary Tommy G. Thompson.

The complaint, filed by the United States Attorney for the Southern District of Texas in U.S. District Court in Houston, charges that VITERA-XT, an ephedra-containing dietary supplement marketed by Houston-based Asia MedLabs, Inc., is an adulterated food as well as an unapproved and misbranded drug, which present an unreasonable risk of illness or injury.

DMAA
(dimethylamylamine)

GMP Requirements

- DSHEA authorized FDA to prescribe good manufacturing practices for dietary supplements
- The cGMP rule (21 CFR Part 111) requires supplement manufacturers to ensure the quality of the supplement and that it is packaged and labeled as specified in the master manufacturing record
    - Ensures that supplements are manufactured consistently as to identity, purity, strength, and composition
    - Provisions related to: facility maintenance, quality controls, cleaning, testing final product or incoming and in-process materials, handling consumer complaints, and maintaining records

GMP Requirements

Subparts of cGMP Rule – Part 111

A	General Provisions
B	Personnel
C	Physical Plant and Grounds
D	Equipment and Utensils
E	Requirement to Establish a Production and Process Control System
F	Production and Process Control System: Requirements for Quality Control
G	Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement
H	Production and Process Control System: Requirements for the Master Manufacturing Record
I	Production and Process Control System: Requirements for the Batch Production Record
J	Production and Process Control System: Requirements for Laboratory Operations
K	Production and Process Control System: Requirements for Manufacturing Operations
L	Production and Process Control System: Requirements for Packaging and Labeling Operations
M	Holding and Distributing
N	Returned Dietary Supplements
O	Product Complaints
P	Records and Recordkeeping

GMP Requirements

Key Provisions in Subpart E

- **Sec. 111.55 What are the requirements to implement a production and process control system?**
  - You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record
- **Sec. 111.65 What are the requirements for quality control operations?**
  - You must implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record
- **Sec. 111.70 What specifications must you establish?**
  - You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record
- **Sec. 111.75 What must you do to determine whether specifications are met?**
  - For a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement

GMP Requirements

Key Provisions in Subpart E

- **Sec. 111.105 What must quality control personnel do?**
  - You must implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record
- **Sec. 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations?**
  - Outlines all the information that should be documented on an MMR, BPR and review and approval thereof
- **Sec. 111.130 What quality control operations are required for returned dietary supplements?**
  - Investigation and disposition decision on rework or disposal
- **Sec. 111.135 What quality control operations are required for product complaints?**
  - Quality control operations for product complaints must include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and follow up action of any investigation performed

Inspections & Enforcement

FDA strives to inspect all domestic facilities once per year but does not due to limited resource

Can be without notice or some limited notice from FDA

FDA Form 482 – Notice of Inspection is issued upon arrival

If FDA wants to document any observations, an FDA Form 483 is issued

No legal requirement to respond to an FDA Form 483, but always best practice to do so

Warning Letter may be issued in cases of repeat or serious GMP violations

Inspections & Enforcement

Products that do not meet the cGMP regulation, based on FDA's observations during a facility inspection, may be deemed adulterated under Section 402(g)(1) of the FD&C Act

- In cases of repeated or egregious GMP violations, a **Warning Letter** can be issued
- Common violations:
  - Failure to establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, as required by Sec.111.70(e)
  - Failure to verify, for a subset of finished dietary supplement batches that you identify through a sound statistical sampling plan (or for every finished batch), that the finished batch of the dietary supplement meets product specifications for identity, purity, strength, and composition, as required by Sec. 111.75(c)
  - Quality control personnel failed to reject the component, dietary supplement, package, or label, when an established specification is not met, or a permitted treatment, an in-process adjustment, or reprocessing was not approved, as required by Sec. 111.113(b)(2)

DOCUMENTATION IS KEY!

Inspections & Enforcement

- In cases of continued violations and lack of GMP compliance, FDA may seek a consent decree, product seizure, or injunction

FDA NEWS RELEASE

Federal officials seize adulterated dietary supplements from Life Rising Corporation due to poor manufacturing practices

Share Tweet Linkedin Email Print

For Immediate Release: June 14, 2019

FDA NEWS RELEASE

Federal judge enters permanent injunction against New York-based dietary supplement manufacturer

Share Tweet Linkedin Email Print

For Immediate Release: March 04, 2021

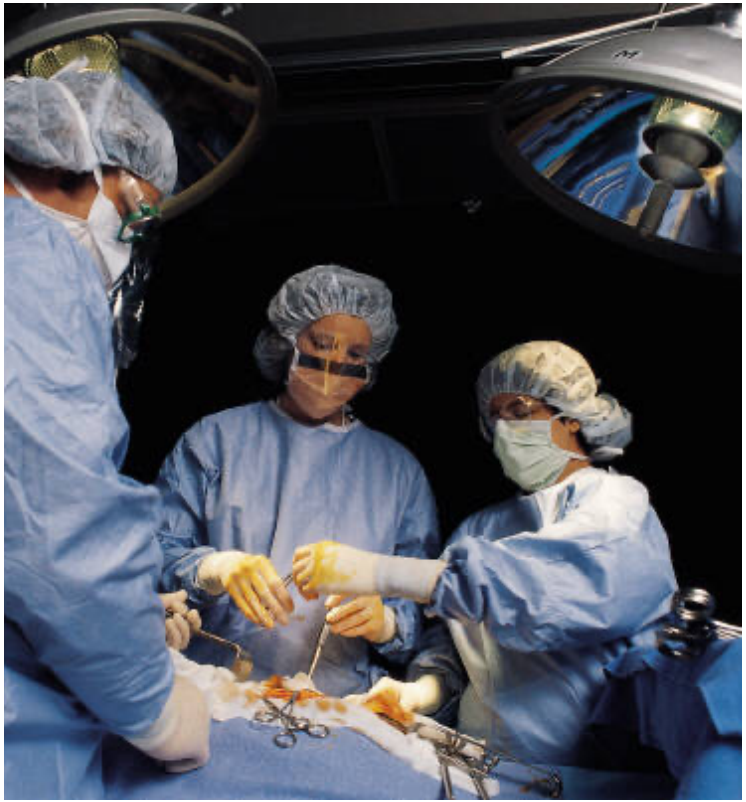
A dietary supplement manufacturer and two of its executives have been ordered by a federal court to stop manufacturing, holding, or distributing any articles of food, including dietary supplements, until they come into compliance with federal dietary supplement current good manufacturing practice regulations and other Federal Food, Drug, and Cosmetic Act (FD&C Act) requirements.

Adverse Event Reporting

The Dietary Supplement and Nonprescription Drug Consumer Protection Act (2006) requires manufacturers to submit to FDA, within 15 business days, any *serious* adverse event reported to the company as being associated with use of a dietary supplement in the U.S.

- The Act refers to the manufacturer, packer, or distributor whose name appears on the label as the “responsible person” required to submit the SAER
- Also required to submit all follow-up reports of new medical information received by the responsible person within one year after the initial report

Adverse Event Reporting



- "Serious Adverse Event" defined by statute as an adverse event that:
  - Results in death; a life-threatening experience; inpatient hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; or
  - Requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome as described above

Recordkeeping Requirements

- Companies are also required to maintain for 6 years records of all non-serious adverse events received
- Must be made available to FDA upon request (typically during FDA facility inspections)

FSMA

- The Food Safety Modernization Act (2011) provided FDA with new enforcement authority
  - Aims to ensure the U.S. food supply is safe by shifting the focus from responding to contamination to preventing it
  - Recognizes the complexity of the global food supply chain
- Because dietary supplements are defined as "food" all FSMA provisions apply, with some exceptions or modifications
  - Dietary supplement manufacturers already subject to cGMP regulations

FSMA: Rules

- Updated cGMPs for food, including a new subpart for Hazard Analysis and Risk-Based Preventative Control (HARPC)
- HARPC requires each facility registered under FSMA to prepare and implement a written food safety plan
    - Includes dietary ingredient/raw material suppliers; subject to Part 117
- Facilities that produce *both* supplements and foods must comply with HARPC requirements, unless an exemption applies

Mandatory Facility Registration

Foreign Supplier Verification Program

- *Modified Requirements*

Third Party Accreditation

Intentional Adulteration of Food

Sanitary Transport Rule

Food Specific:

- *Preventative Controls Rule*
- *Produce Safety Rule*

FSMA: Enforcement Tools

FSMA provides FDA with several enforcement tools applicable to supplements

E.g., Authority to mandate product recalls, suspend facility registrations, and to investigate and detain products

Requires biennial facility registration and expands FDA access for facility and recordkeeping inspections

Expands requirements for foreign supplier imports

Prior notice must be filed with FDA

Imported products subject to inspection upon entry into the U.S.

Thank You!

Rend Al-Mondhiry
Rend@AminTalati.com
1.202.918.7852

Your training partner for regulatory affairs
Regulatorytrainingdirect.com

E-Learning Training | LIVE Training | Regulatory News

AMIN | TALATI
WASSERMAN