

**CHAPTER 21 – FOOD COMPOSITION, STANDARDS, LABELING, AND ECONOMICS**

<b>SUBJECT:</b> <b>DIETARY SUPPLEMENTS – FOREIGN AND DOMESTIC INSPECTIONS, SAMPLING, AND IMPORTS</b>		<b>IMPLEMENTATION DATE:</b> <b>09/30/2020</b>
<b>DATA REPORTING</b>		
<b>PRODUCT CODES</b>	<b>PRODUCT/ASSIGNMENT CODES (PAC)</b>	
All Human Dietary Supplements  Industry Code: 54  Subclass Code: B, C, and Y only  USE APPROPRIATE PRODUCT CODES	REPORT PROGRAM ACTIVITIES UNDER THE FOLLOWING PAC CODES:  <b>21008</b> all sample collection and analysis  <b>21008F</b> all full scope inspections of dietary supplement manufacturers under 21 CFR part 111  <b>21008D</b> all inspections of dietary supplement distribution facilities under 21 CFR part 111  <b>21008L</b> all limited focus inspections of dietary supplement manufacturers under 21 CFR part 111  <b>21008W</b> all inspections of dietary supplement warehouse facilities under 21 CFR part 111  <b>21R829</b> all activities involving nutritional health fraud	

**FIELD REPORTING REQUIREMENTS:**

The Office of Regulatory Affairs (ORA) field division completes the Establishment Inspection Report (EIR), including an inspection classification consistent with Field Management Directive (FMD) 86 and FDA policies including this compliance program, within ORA established timeframes. The ORA division files the inspection documents electronically no later than 30 working days from the close of the inspection using the appropriate module (eNSpect, or Compliance Management System (CMS)) accessible to both ORA and Center for Food Safety and Applied Nutrition (CFSAN).

ORA divisions should, as soon as practical, report significant inspection findings into eNSpect, as per the Investigations Operations Manual (IOM). For inspections initially classified as Official Action

Indicated (OAI) due to failure to comply with Dietary Supplement Current Good Manufacturing Practice (CGMP) regulation in 21 CFR part 111, submit the written classification analysis and electronic documents to CFSAN's Office of Compliance (OC), Division of Enforcement (DE) for evaluation through CMS in accordance with Regulatory Procedures Manual (RPM) timeframes.<sup>1</sup>

During an inspection, if you obtain information pertaining to inadequate notification of mandatory reporting requirements (e.g. reporting of serious adverse events<sup>2</sup>, FDA notification of New Dietary Ingredients<sup>3</sup>, FDA notification of structure/function claims<sup>4</sup>) report under separate headings in the EIR. Report all operations, foreign, domestic and import, under the PAC(s) in this compliance program, see [Table 1-1](#).

Time spent reviewing import labels that does not result in a sample collection must be reported as an import label examination (LEX) for labeling (LBL) using the appropriate PAC(s) from above. The ORA divisions should use this revised compliance program for all sample collections and CGMP inspections satisfying the statutory obligation for inspections of dietary supplement production.

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<sup>1</sup> For further information see Part V Regulatory/Administrative Strategy

<sup>2</sup> Federal Food, Drug and Cosmetic Act (FD&C Act), § 761

<sup>3</sup> FD&C Act, § 413

<sup>4</sup> FD&C Act, § 403(r)(6)

## Contents

PART I – BACKGROUND .....	5
PART II - IMPLEMENTATION .....	6
1. Objectives .....	6
2. Program Management Instructions .....	6
PART III - INSPECTIONAL .....	11
1. Operations .....	11
A. Inspections (Domestic and Foreign).....	11
B. Investigations.....	15
C. Domestic Field or Label Exams .....	15
D. Sample Collections (Domestic).....	17
E. Sample Collections and Label Examinations (Import) .....	20
F. Import Activities.....	21
G. Shipping.....	22
2. Reporting.....	22
PART IV - ANALYTICAL .....	23
1. Analyzing Laboratories.....	23
2. Analyses to be Conducted.....	23
3. Methodology .....	23
4. Reporting.....	26
PART V - REGULATORY/ADMINISTRATIVE STRATEGY .....	27
1. Findings.....	27
2. Actions .....	27
3. Regulatory Follow-Up .....	33
PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS .....	35
1. References.....	35
2. Attachments .....	36
3. Program Contacts.....	36
PART VII - CENTER RESPONSIBILITIES .....	37
ATTACHMENT A – EXEMPTIONS FROM NUTRITION LABELING ("SUPPLEMENT FACTS" LABEL).....	38
ATTACHMENT B – STANDARD LANGUAGE FOR WARNING LETTERS IN AREAS OF EMPHASIS .....	39
ATTACHMENT C – LIST OF INGREDIENTS OF CONCERN FOR COVERAGE DURING INSPECTIONS .....	47
ATTACHMENT D – GUIDANCE ON EVIDENCE DEVELOPMENT AND DOCUMENTATION TO SUPPORT REGULATORY ACTION.....	53

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ATTACHMENT E – CGMP REQUIREMENTS APPLICABLE TO OPERATIONS  
PERFORMED BY FIRM..... 54

## PART I – BACKGROUND

In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA). The term “dietary supplement” is defined in section 201(ff) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as a product (other than tobacco), intended to supplement the diet, that bears or contains one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract or combination of any ingredient described above.

The dietary supplement market in the United States has grown significantly since the enactment of DSHEA and is worth more than \$40 billion, up from \$4 billion in 1994. The number of dietary supplement products on the market has exponentially increased from approximately 4,000 products on the market in 1994 to estimates ranging from 50,000 to more than 80,000 different products on the market in 2019. These products are produced through a global supply chain that includes more than 10,000 facilities.

The Current Good Manufacturing Practice (CGMP) regulation for manufacturing, packaging, labeling, or holding operations for dietary supplements was published on June 25, 2007.<sup>5</sup> A primary objective of FDA’s dietary supplement inspection program is to ensure that dietary supplement products meet federal standards for quality and accurate labeling. Dietary supplements are subject to certain requirements of The FDA Food Safety Modernization Act (FSMA)<sup>6</sup> and applicable sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including section 761 (Serious Adverse Event Reporting for Dietary Supplements).

This compliance program provides for sampling and surveillance inspection coverage of dietary supplement manufacturing establishments subject to the requirements of CGMP as per 402(g) of the FD&C Act, FSMA and implementing regulations. The focus of surveillance inspections is on compliance with CGMP to ensure products are not adulterated or misbranded – including those products making drug claims or that contain other misleading claims, products that contain new dietary ingredients or unsafe food additives, and other risks. Increased surveillance of dietary supplements in the areas of concern is warranted. Current sampling initiatives include sampling of raw botanical ingredients and finished dietary supplements containing botanical ingredients that are at risk for contamination with elevated levels of toxic elements, dietary supplements spiked with drug ingredients not declared on their labels, and dietary supplements labeled as containing other unlawful ingredients.

FDA will use information gathered from sample collections and surveillance inspections to, among other things, adjust FDA’s regulatory program activities to protect and promote the public’s health. The inspectional guidance in this program is structured to provide for efficient use of resources devoted to routine surveillance coverage, with consideration of program priorities. It also provides guidance for conducting for-cause inspections as appropriate.

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<sup>5</sup> Refer to 72 FR 34751, 21 CFR 111

<sup>6</sup> FSMA - <https://www.fda.gov/food/food-safety-modernization-act-fsma/full-text-food-safety-modernization-act-fsma#SEC113>

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## PART II - IMPLEMENTATION

### 1. Objectives

The goal of this compliance program is to ensure that establishments consistently manufacture dietary supplements of acceptable quality and minimize consumer's exposure to adulterated and/or misbranded dietary supplements. The objectives of this program are:

- To conduct inspections of domestic and foreign dietary supplement manufacturers subject to 21 CFR part 111 within mandated FSMA inspection frequencies and enforcement follow-up timeframes.
- To collect and analyze domestic and import samples to determine if they are in compliance with the requirements of the FD&C Act.
- To enforce dietary supplement regulations for products that are not in compliance with the FD&C Act amended by the Dietary Supplement Health and Education Act (DSHEA) and verify implementation of corrective actions in follow-up inspections or investigations.
- To collect information to determine if dietary supplements are being labeled in accordance with applicable requirements.
- To collect compliance information for FDA to modify or develop enforcement strategies.

### 2. Program Management Instructions

#### A. Inspection Priorities

There are four different inspectional approaches based on FDA resource, priorities, and dietary supplement establishment operations:

- Full Scope Manufacturing Inspection – will cover compliance with all applicable CGMP requirements at firms that manufacture dietary supplements.
- Limited Focus Manufacturing Inspection – will at a minimum cover CGMP compliance with the required elements listed in Part III at firms that manufacture dietary supplements.
- Distributor Inspection – will cover compliance with the applicable CGMP requirements for firms that distribute, but do not manufacture, products, including firms package and/or label their own dietary supplements that another firm manufactures.
- Warehouse Inspection – will cover compliance with the applicable CGMP requirements for firms that hold, and possibly distribute, dietary supplements owned by someone else, but do not perform manufacturing, packaging, or labeling operations.

CFSAN will provide a list of dietary supplement firms due for inspection during a fiscal year inspectional cycle under FD&C Act section 421 (FSMA 201) to ORA divisions prior to the beginning of each fiscal year. This list will identify the likely scope of inspection under dietary supplement CGMP for each facility (e.g. full scope manufacturer, limited focus manufacturer, distributor, warehouse), when possible. The division may change the scope of inspection based on the type of operations performed by the firm, or those observed during the inspection.

The following factors should guide prioritization of firms for full scope dietary supplement inspections:

- Firms that are responsible for a Class 1 or Class 2 recall since the previous inspection.
- The firm's previous inspection was classified "Official Action Indicated" (OAI).
- The firm has no FDA inspectional history.
- The firm is known to manufacture high-risk dietary supplements. See description of high-risk dietary supplement below.
- Firms that are implicated in an event that may impact public health. The FDA may obtain this information from a variety of sources, including, but not limited to, federal, state, local, or tribal partners; foreign competent authorities; from the Adverse Event Reporting; from consumer complaints, or from other intelligence information available to CFSAN.

When possible, firms manufacturing high-risk dietary supplements should be given priority. Firms with high-risk dietary supplements include, but are not limited to:

- Firms manufacturing botanical supplements: the botanical ingredients may contain contaminants, such as toxic elements or microbial pathogens. Additionally, botanical extracts can present challenges for identity and strength testing.
- Firms manufacturing dietary supplements that contain bovine ingredients: certain cattle materials are prohibited from use in human food (21 CFR 189.5); ingredients with bovine origin should be adequately processed to remove the prohibited material. Additionally, bovine ingredient should originate from countries with designation granted by the Agency.
- Firms manufacturing dietary supplements that contain potential new dietary ingredients: new dietary ingredients without the necessary safety assessment could pose a public health risk. FD&C Act 413(a) states that a dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets the requirements found under 413(a)(1) or 413(a)(2).
- Firms manufacturing multiple dosage forms: e.g. powder, liquid, gummy, or softgel dosage forms.

### **Product Selection During Inspection**

Products should be selected for review using a risk-based approach including quality indicators (recalls, complaints, adverse events, out-of-specification (OOS), etc.), target populations (pediatric, pregnant, geriatric), sales volume, and manufacturing complexity. Priority should be given to dosage forms (capsules, tablets, liquids, powders, gummies, etc.) not previously covered during an FDA inspection. If more than one product is selected for coverage during the inspection, coverage of different dosage forms should be considered. It is important that the products chosen fit the definitional requirements of a dietary supplement, as defined in section 201(ff)(1) and (2): contains at least one dietary ingredient, intended to be ingested, and labeled as a dietary supplement. Since this determination can be fact-dependent and critical factors may not be readily apparent, investigators are encouraged to consult with

Center representatives early in an inspection, if not before, to ensure selection of appropriate product(s).

Selection of components to cover during the product reviews should consider the ingredients identified in [Attachment C](#). If the product selected for review uses different component types (botanical, vitamin, mineral, animal derived, etc.), the components selected for review should include components of different types.

## B. Planning Instructions

### (1) Inspections

Facilities without a previous FDA inspection, or that are currently OAI status, should be inspected as full scope inspections. Facilities with previous NAI or VAI status can be inspected as limited focus inspections, depending on the other factors mentioned in identifying which firms to prioritize for full scope dietary supplement inspections above. For-cause inspection can be performed as full scope inspection or a limited focus inspection with focus on the issues that triggered the inspection.

### (2) Sampling

Samples may be collected during inspections covered by this compliance program for both for-cause and surveillance, and under routine surveillance sampling programs such as the [Sample Collection Operation Planning Effort \(SCOPE\)](#).

If a facility is involved in ongoing compliance activities or the current inspection may be classified as OAI, the division should consult with their Compliance Branch to determine whether collection of samples for the surveillance purpose is appropriate (see Part IV for additional information).

### (3) Resources and Reporting

Divisions should try to coordinate resources so that inspections conducted under this program also meet inspection obligation for other programs. For example, if the dietary supplement firm also manufactures conventional food, a conventional food CGMP inspection or PCHF inspection may be performed at the same time. Please see [Table 1](#) for additional resource and reporting information.

<b>Reporting PAC</b>	<b>Code</b>	<b>Description</b>
	<b>21008</b>	Sample Collection and Analysis (all examinations and sample collections)
	<b>21008F</b>	DS full scope inspections at manufacturers under 21 CFR 111
	<b>21008D</b>	DS inspections of distributors under 21 CFR 111
	<b>21008L</b>	DS limited focus inspections of manufacturers under 21 CFR 111
	<b>21008W</b>	DS inspections of warehouse facilities under 21 CFR 111
	<b>21R829</b>	All activities involving nutritional health fraud

<b>Planning PAC</b>	<b>21008F</b>	DS full scope inspections at manufacturers under 21 CFR 111
	<b>21008L</b>	DS limited focus inspections of manufacturers under 21 CFR 111
	<b>21008</b>	DS Sample Collections and Analysis
<b>Inspection Op. Code</b>	11 (foreign), 12 (domestic)	
<b>Investigation Op. Code</b>	15 (foreign), 13 (domestic)	

### C. Interactions between Compliance Programs

If a facility is inspected under this program and the covered food product is subject to additional regulations, compliance programs, or assignments outside the scope of this compliance program, then additional inspection and reporting requirements should be covered per the respective interacting programs.

This compliance program may have some interactions with the following CPGMs. Use the appropriate PAC when reporting sample collections under this compliance program:

- Preventive Controls and Sanitary Human Food Operations 7303.040
- Juice HACCP Inspection Program, 7303.847
- Domestic Acidified and Low-Acid Canned Foods Program, 7303.803a
- Domestic and Import Food Additives and Color Additives, 7309.006
- Medical Foods – Import and Domestic, 7321.002
- Pesticides and Industrial Chemicals in Food (Domestic and Import), 7304.004
- Toxic Elements in Food and Foodware – Import and Domestic, 7304.019
- Foreign Supplier Verification Program (currently an assignment)
- Sanitary Transportation Inspections (currently an assignment)

### D. Food Defense Measures and Food Facility Registration

Field inspection staff should confirm that each facility inspected under this program has a current food facility registration per the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act) and Section 415 of the FD&C Act. If registration information obtained during the inspection (foreign and domestic) is different from the information in the Food Facility Registration Module (FFRM), send an email to [CFSANFoodFacilityRegistration@fda.hhs.gov](mailto:CFSANFoodFacilityRegistration@fda.hhs.gov) in accordance with [IOM](#) subchapter 5.4.1.5.2 ‘Food Facility Registration Resources’.

### E. Interaction with Other Federal Agencies, State and Local Counterparts, and Foreign Authorities

#### (1) Federal Agencies

Follow [IOM](#) subchapter 3.1.3.2 ‘Discussion with Federal Inspector’ when federal officials from other agencies are present during FDA inspections or investigations. See [IOM](#) subchapter 3.2 ‘Federal Agency Interaction’ for a list of Memorandums of Understanding (MOU) between the FDA and other Federal agencies that may be applicable to inspections

conducted under this program [225-10-0010](#) and [225-19-032](#). A complete list of MOUs may be found [here](#).

(2) State and Local Counterparts

Divisions will collaborate with commissioned State agencies to make them aware of the requirements of this program and deadlines for deliverables. Divisions will offer State agencies opportunities to accompany FDA on inspections or assist as necessary and when possible this communication should be initiated no later than two weeks prior to an inspection.

(3) Foreign Authorities

Follow ORA/DFHAFO procedures when foreign competent authorities are present during FDA foreign inspections or investigations.

F. When to Contact Other Offices within the FDA

**Regulator Technical Assistance Network (rTAN)**

The rTAN is a resource primarily for FDA and state field inspection staff to request information assistance during inspections. It is not intended to replace the current enforcement communication mechanism between field inspection staff, supervisors and compliance officers or states.

The rTAN is an information assistance system designed to connect field inspection staff with SMEs to get answers and clarification on FSMA rule interpretation and commodity specific questions as needed. A list of rTAN commodity-specific SMEs, ORA National Expert SMEs, and lead program contacts (rTAN list) can be found in the [resource library](#) or [open-access DS SharePoint site](#). Field inspection staff should submit inquiries through the rTAN e-mail inbox at [rTANWorkgroup@fda.hhs.gov](mailto:rTANWorkgroup@fda.hhs.gov). If an inspection is in-progress and an answer is required as soon as possible, field inspection staff should indicate that in the e-mail subject heading.

While the rTAN e-mail inbox is the preferred method of communication for ongoing inspections, FDA field inspection staff may also contact the designated SMEs from the rTAN to request that they operate in a reasonable “on call” capacity during an inspection window. This will ensure that SMEs are available to answer questions or respond to concerns during an inspection. If field inspection staff want to reach out to several SMEs, please send one email and include everyone on it to minimize duplication of effort and to ensure consistency of guidance.

G. Resource Instructions

- Resources for sample collections, analyses, import field/label exams, and emerging issues for dietary supplements are provided in the [ORA Field Workplan](#).
- Resources will be allocated through a prioritization process.

## PART III - INSPECTIONAL

### 1. Operations

Inspections conducted under this compliance program should evaluate the establishment's adherence to the Dietary Supplement CGMP, other applicable regulatory requirements, and the FD&C Act generally.

Information on how to respond to the FDA 483 *Inspectional Observations* should be provided to the facility's management. **For foreign inspections, firm's responses to FDA 483 should be sent to [FDA483responseinternational@fda.hhs.gov](mailto:FDA483responseinternational@fda.hhs.gov).** Field inspection staff must inform the firm that the adequacy of their response to the FDA 483 may impact FDA's determination of the need for follow-up action. FDA expects the firm to respond to the FDA 483 within 15 business days of the end date of the inspection.

During inspections at U.S. facilities that are also importers, the [Foreign Supplier Verification Programs: What Do Manufacturers/Processors Covered by the PC Supply-Chain Program Need to know about FSVP?](#) document should be provided to firm management.

#### A. Inspections (Domestic and Foreign)

##### **Manufacturing Inspections**

Manufacturing inspections will be conducted at firms that conduct some or all of the manufacturing steps for a dietary supplement. Manufacturers can be assigned as a limited focus or full scope inspection:

- **Full Scope Manufacturing Inspections**

Full scope inspections cover compliance with all CGMP requirements. Coverage includes all required elements listed below, see [Attachment E](#) for additional detail as to what the elements include, and any other CGMP requirements applicable to the operations the firm performs. At least two finished dietary supplement products must be covered during the product review. Cover additional products if significant deficiencies are found during the product review.

- **Limited Focus Manufacturing Inspections**

Limited focus inspections cover compliance with all CGMP requirements but for a limited number of products. Coverage includes all required elements listed below, see [Attachment E](#) for additional detail as to what the elements include, and any other CGMP requirements applicable to the operations the firm performs. At least one finished dietary supplement product should be included in the product review. Cover additional products if significant deficiencies are found during the product review.

Field inspection staff should notify division management when significant deviations are observed pertaining to any required element to determine if a full scope inspection is warranted.

##### **Required Elements**

1. Labeling Review – Evaluate the product labels, printed promotional materials, and online presence including websites and social media for the use of disease claims that would make the products unapproved new drugs. Verify labels comply with the nutrition

- labeling (“Supplement Facts” label), adverse event reporting, structure/function claim reporting, allergen labeling, and other applicable [labeling requirements](#).
2. Requirements of Quality Control – Review written procedures for the responsibilities of quality control and ensure quality control personnel conduct required activities.
  3. Quality Indicators – Review recalls, quality complaint investigations, adverse events, laboratory out-of-specification (OOS) investigations, deviation investigations and returned products.
  4. Facility and Equipment – Conduct a walkthrough inspection of areas where components and finished dietary supplements are exposed to the environment and evaluate the sanitation and maintenance of the facility and equipment. Evaluate the potential for contamination, allergen cross-contact, and pests. Determine the adequacy of employee hygiene.
  5. Product Review
    - a. Master Manufacturing Record – Review the master manufacturing record and determine whether it contains required information and identifies appropriate specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement.
    - b. Batch Record – Review the executed batch record and determine whether it contains required information and documents specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement are met.
    - c. Components – Review at least three components used in the product to ensure appropriate specifications have been established. Review testing data or documentation showing component specifications are met. Determine whether methods used to verify specifications are appropriate and scientifically valid.
    - d. Finished Dietary Supplement – Ensure appropriate finished dietary supplement specifications have been established. Review testing data or documentation showing finished dietary supplement specifications are met. Determine whether methods used to verify specifications are appropriate and scientifically valid.

### **Distributor Inspections**

Distributor inspections should be conducted at firms that contract out some or all of their manufacturing but are ultimately responsible for introducing or causing introduction of the finished dietary supplement into interstate commerce. At least two finished dietary supplement products should be included in the product review. All required elements applicable to the distributor’s operations should be covered.

### **Required Elements**

1. Labeling Review – Evaluate the product labels, printed promotional materials, and online presence including websites and social media for the use of disease claims that would make the products unapproved new drugs. Verify labels comply with the nutrition

labeling (“Supplement Facts” label), adverse event reporting, structure/function claim reporting, allergen labeling, and other applicable [labeling requirements](#).

2. Responsibility – Identify the contract manufacturers used by the distributor to manufacture their products. Document the responsibilities for applicable CGMPs established between the distributor and contract manufacturers.
3. Product Review – Evaluate the distributors quality control procedures. Document the operations of the quality control personnel for the selected products including how they determine whether the product has been manufactured in accordance with CGMP, how they conduct a material review and make a disposition decision, and how they handle returned products and reserve samples.
4. Complaints and Adverse Event Reporting – Review procedures for handling customer complaints and adverse events. Evaluate investigations of customer complaints and determine if adverse events were reported to FDA if applicable.
5. Additional coverage should be provided to all applicable responsibilities based on the operations the distributor performs (packaging and labeling, holding, facilities, equipment, etc.) and the responsibilities assigned to the distributor as identified in distributor required element #2 (establishment of specifications, etc.).

### **Warehouse Inspections**

Warehouse inspections will be conducted at firms that hold dietary supplements owned by someone else, but do not perform manufacturing, packaging, or labeling. These firms may also distribute dietary supplements owned by someone else. All required elements applicable to the operations must be covered.

#### **Required Elements**

1. Physical Plant and Grounds - Conduct a walkthrough inspection of areas where finished dietary supplements are held. Evaluate the sanitation, maintenance, and pest control of the facility.
2. Holding - Verify written procedures are established and followed to ensure dietary supplements are held to prevent the mix-up, contamination, or deterioration of dietary supplements, including holding under appropriate conditions of temperature, humidity, and light.
3. Distribution – Ensure dietary supplements are distributed under conditions that will protect the dietary supplements against contamination and deterioration. Verify distribution records are kept.
4. Returns – Ensure returned product is identified and quarantined until quality control personnel conduct a material review and make a disposition decision according to established written procedures.

### **Adverse Event Reporting**

[CFSAN Adverse Event Reporting System \(CAERS\)](#) is a database that contains information on adverse event reports submitted to FDA. Verify that the firm has a record keeping system in place for maintaining records of adverse event reports. Determine if the firm has a process in place to report serious adverse events, if the firm has submitted any reports to the FDA since the last inspection, and if any serious adverse event reports exist but were not submitted.

Review the labels for up to five different dietary supplement products manufactured, packed, or distributed by the firm being inspected, to assure that the labels bear a domestic address or domestic phone number, (i.e. either a complete address within the US to include firm name, street address (or P.O. Box), city, state and zip code or complete telephone number to include the area code) through which the person responsible for submitting reports of serious adverse events to the Agency can receive the reports. Labels lacking the information described above are misbranded; divisions should follow procedures noted in Part V.

### **Edible Ruminant Products from BSE Affected or At-Risk Countries**

Bovine-derived ingredients cannot be used in dietary supplements if they adulterate the product under any provision of Section 402 of the Act. If an investigator encounters any one of the conditions below related to use of a bovine-derived ingredient, the following evidence must be collected and forwarded to CFSAN for further regulatory consideration.

- 1) A bovine-derived ingredient is a prohibited cattle material under 21 CFR 189.5(a) if it is a specified risk material that has not been inspected and passed for human consumption by a competent authority or is otherwise a prohibited material under 21 CFR 189.5(a). Affirmative evidence of the use of prohibited cattle material must be collected.
- 2) If the firm is using bovine-derived ingredients, they must have records to show that the food is not manufactured from, processed with, or does not otherwise contain prohibited cattle materials (21 CFR 189.5(c)). Documentation of the lack of these records must be collected.
- 3) Under the dietary supplement CGMP regulations, firms must establish specifications for animal-derived ingredients that are necessary to ensure the quality of the dietary supplement. Firms must also take necessary actions to determine that specifications are met. If such specifications are not established or met, collect adequate documentation of the deficiency.

### **Dietary Supplements Containing Ephedrine Alkaloids**

- 1) If the product label states that it contains “ephedra,” attempt to determine from the firm whether they have evidence that it does not contain ephedrine alkaloids. Determine whether the firm relies on certificates of authenticity or other assurances from suppliers that the ephedra species used does not contain naturally occurring ephedrine alkaloids or has laboratory evidence that the product does not contain ephedrine alkaloids.
- 2) If a product claims to contain ephedrine alkaloids or contains “ephedra” and the firm

does not appear to have evidence that it does not contain ephedrine alkaloids, the inspection should specifically cover the following items:

- Collection of interstate documentation of the products shipped from the manufacturer or supplier to the firm (this information should be tied into an affidavit).
  - From whom does the firm obtain products?
  - Where does the firm warehouse their products?
  - What volume of product do they buy and sell?
  - Do they sell to consumers only or also to other distributors?
  - Is the product being offered for sale through sponsored websites?
  - Collect all labeling, ads, and promotional material currently used.
- 3) If the firm does not manufacture the products, the division should attempt to get information from the firm about their supplier. If the suppliers are not located in the same division, the division should issue an assignment to the home division of the supplier for follow-up.
- 4) If the investigator can document that the product is being offered for sale, proceed with the collection of an official sample as instructed below under Part III(1)(D)(1), Area of Emphasis #5 (Ephedrine Alkaloid Analysis).

## B. Investigations

Domestic or foreign investigations (OP 13 or OP 15, respectively) may be performed at facilities covered by this program. See [IOM](#) subchapter 8.10 *General Investigation Reporting* for guidance covering how to conduct and report an investigation.

If a domestic or foreign facility assigned for inspection is no longer operational, does not manufacture products that fall under FDA jurisdiction, or cannot be inspected for any other reason, an investigation may be created by utilizing the washout conversion function in eNSpect. Administrative information should be updated in Firm Management Services (FMS) as appropriate.

## C. Domestic Field or Label Exams

Products shipped in bulk form, not distributed to consumers in such form, and used in the manufacture of other dietary supplements or that are to be processed, labeled, or repacked at a site other than where originally processed or packed are exempt from the requirements for nutrition labeling ("Supplement Facts" label) (21 CFR 101.36(h)(3)). However, they must contain other mandatory elements of the food label, specifically, the products' common or usual name, the name and place of business of the manufacturer or other responsible firm, a list of ingredients, and the net contents.

Investigators must review the [list of firms that have filed for a small business nutrition labeling exemption](#) prior to conducting inspections to determine whether the firm has been

issued an exemption from CFSAN. Investigators must verify the firm's status with firm management after issuing the FDA 482, but prior to conducting any field exams. Do not conduct field exams in firms that are exempt from compliance.

**NOTE: In accordance with 21 CFR 101.9(j)(1)(i), a nutrient content claim, a health claim, or any other statement about the nutrient content or benefits of the product (other than ingredient statements) on a dietary supplement label negates the exempt status of the product and triggers the requirement for nutrition labeling (“Supplement Facts” label).**

Specific questions about the exempt status of a domestic firm, importer, or broker should be directed to CFSAN/ODSP (HFS-810), (240) 402-2878 and industry web-based submission link: <https://www.cfsanappsexternal.fda.gov/scripts/NLE/client/login.cfm>.

Review the label of 2-3 products focusing on the following Areas of Emphasis. **Refer to the references provided in Part VI of this program for additional information to assist during reviewing labels under each Area of Emphasis.**

### Areas of Emphasis

- 1) Products or ingredients promoted in the products that claim to diagnose, mitigate, treat, cure, or prevent disease. (Sections 301(d), 505(a) and 502(f)(1) of the FD&C Act).

Note: The Agency will, on a case-by-case basis, consider enforcement actions against products that bear disease claims. Investigators should review claims made for dietary supplements on labels or in labeling, including the firm's website and social media accounts. Products that bear disease claims or that appear to bear unauthorized health claims (e.g., health claims are [authorized by regulation](#) and are about reduction in risk of a disease or health condition and involves a food or food component) that do not meet the requirement should be referred to CFSAN for evaluation.

- 2) Products that contain a new dietary ingredient (NDI) without the required NDI notification submission (Sections 413 of the FD&C Act) see [Attachment C](#), and products that contain ingredients listed on the [Dietary Supplement Ingredient Advisory List](#).
- 3) Products that bear authorized health claims or nutrient content claims that do not qualify for making the claims. For example, for the approved calcium and osteoporosis, and calcium, vitamin D, and osteoporosis claims, phosphorus content cannot exceed calcium content. (Refer to [FDA Food Labeling Guide](#), Appendix C - Health Claims)
- 4) Products suspected of containing prohibited cattle (bovine) materials, including failure to maintain adequate records by firms that manufacture or process dietary supplement containing cattle derived material to support the materials are free from bovine spongiform encephalopathy (BSE).

- 5) Products that are labeled to contain or declare a source of ephedrine alkaloids.
- 6) Products that are marketed as dietary supplements but fail to bear a statement of identity on the principal display panel (dietary supplement, herbal supplement, etc.), or nutrition label, i.e., the absence of "Supplement Facts" on the label and the product is not covered by an exemption. (see above list for exempt domestic firms and importers).
- 7) Products that fail to disclose a major food allergen.
- 8) Products that declare "Siberian ginseng" (Section 403u of the FD&C Act).  
The term "ginseng" may only be considered to be a common or usual name (or part thereof) for any herb or herbal ingredient derived from a plant classified within the genus *Panax*, and only labeling or advertising for herbs or herbal ingredients classified within that genus may include the term "ginseng."
- 9) Products that fail to bear other mandatory label information (e.g., ingredient statement, domestic address or phone number for serious adverse event reporting, name and place of business of the manufacturer, packer, or distributor, net quantity of contents).
- 10) Products that fail to bear nutrition ("Supplement Facts" label) labeling or with significant format deviations (21 CFR 101.36).
- 11) Products in solid dosage form with added iron or iron salts that are claimed in the supplement facts label but fail to bear the required warning statement (21 CFR 101.17(e)(1)).

#### D. Sample Collections (Domestic)

Compliance (for-cause) and surveillance samples may be collected during inspections covered by this compliance program. These samples may be covered under interacting compliance programs listed in [Part II\(2\)\(C\)](#) of this program, under routine surveillance sampling programs such as the [Sample Collection Operation Planning Effort \(SCOPE\)](#), under CFSAN or ORA [active assignments](#), or as directed for compliance purposes.

Documentary samples will generally consist of the label and any labeling that is available with the product at time of purchase; this may include labeling and marking information available on the product page for the website where the product is sold. No physical sample is required. When the configuration of the container makes it difficult to determine the total amount of label space available to bear labeling it will be necessary to collect the actual container along with the label. **If the firm operates a website for dietary supplement product(s), Divisions should review the product website page for any labeling information available.**

##### 1) Compliance Samples

###### **Areas of Emphasis Nos. 1, 2, 6-11**

- a) The sample will consist of an original label, or quality photograph (and one product container, if warranted) for the product being sampled and associated labeling, including the firm's website where products are promoted with disease claims and offered for sale. This is a documentary sample only; no physical sample is required.

Prepare a Collection Report (C/R) for each product label collected and mark as "Documentary" in the **Sample Type** field.

- b) For samples collected for undeclared allergens sample collection must include documentation of allergenic raw material and evidence that the allergen is undeclared, e.g., raw material label, formulation of final product, manufacturing and batching records and final product label.
- c) Indicate "Compliance" in the **Basis** field of the C/R. Under **Reason for Collection** indicate "Label Review Only."
- d) Send the sample to your compliance branch for label review, sample classification, and regulatory consideration.

### **Area of Emphasis No. 3 (Nutrient Analysis)**

In order to make authorized health claims or nutrient content claims, products must meet certain nutritional requirements. Refer to [21 CFR 101](#) Subparts C-F for specific requirements for nutrient content claims and health claims.

Investigators should also refer to FDA's website for both authorized health claims and [nutrient content claims](#) (relative or comparative claims) to determine if the amount of the nutrient listed on the nutrition label qualifies the product to make the claim. If analysis is necessary to verify the level of the nutrient a physical sample must be collected.

- a) The sample will consist of 24 consumer size retail packages, 2 packages from each of 12 randomly selected shipping cases or 10% of the number of packages in the same inspection lot (collected in duplicate), whichever is smaller. Do not commingle lots.

Note: This sample size includes the 702(b) portion. Number the subsamples as 1a, 1b, 2a, 2b, etc., to separate the units for analysis from units that comprise the 702(b) portion.

- b) Prepare a Collection Report (C/R) for each sample collected and mark as "Official" in the **Sample Type** field.
- c) Indicate "Compliance" in the **Basis** field of the C/R. Under **Reason for Collection** indicate "For <insert Nutrient(s) forming the basis for the claim> analysis."

### **Area of Emphasis No. 4**

FDA regulations prohibit the use of certain cattle materials in food, including dietary supplements (see **21 CFR 189.5 and Part I, Background of this program for further information**). FDA regulations at 21 CFR 189.5(c), include record keeping that demonstrates that products are not made with prohibited cattle materials. Records must be maintained for 2 years and FDA must be allowed to inspect and copy them.

- a) The EIR and supporting documents will be reviewed by CFSAN/OC/DE, a determination will be made on a case-by-case basis whether additional regulatory follow-up is necessary.

### **Area of Emphasis No. 5 (Ephedrine Alkaloid Analysis)**

Products suspected of containing ephedrine alkaloids must have a physical sample sent to the lab for confirmation of the presence of ephedrine alkaloids, as an Official Sample.

- a) For products that potentially contain a source of ephedrine alkaloids, each sample size shall consist of three retail units of each product.
- b) Collect a maximum of 5 samples, each sample consisting of a unique lot number.
- c) Include information on the size of each lot sampled on the collection report.
- d) If the product is manufactured or warehoused at another location, this must be indicated on the collection report.

## 2) Surveillance Samples

**Sampling should be coordinated to be collected onsite during inspections.** Retail samples should only be collected when inspections do not generate sufficient samples to meet division workplan obligations. See [IOM](#) chapter 4 - Sampling for guidance covering how to collect and report a sample.

### Nutrient Analysis

For nutrient analysis, collect 3 units (each unit must contain a minimum of 12 servings) of the product. For example, 3-2 lb. tins; 3-100 tablet bottles; 3-30 capsule packets; 3-12 bar packages. Contact [Nutrient Analysis Branch](#) at The Southeast Food and Feed Laboratory (SFFL) if necessary and if there are any additional questions on sample size.

Further, investigators should consider the following information for the collection of samples for nutrient analysis:

- a) Collect for nutrient analysis only those vitamin, mineral, and protein supplements or combination vitamin/mineral supplements that have at least one nutrient declared on the label at or above 25% of the Reference Daily Intake (RDI) or Daily Reference Value (DRV).  
*Note: For each nutrient declared at or above 25% of RDI, include on the collection report a statement for each nutrient whether the nutrient is naturally occurring or added. This information is necessary to support the appropriate charge should analysis indicate a nutrient deficiency.*
- b) If inspections do not generate sufficient samples to meet division workplan obligations domestic and domestic-import surveillance samples may be collected at the retail level. **Attempt to sample products that have been manufactured within the collecting division so that follow-up compliance sampling with interstate documentation may be conducted, if necessary.** However, if it isn't possible to generate samples in this manner, select any appropriate product in line with the collection guidance below.
- c) In selecting samples for collection, consider factors which might result in lower nutrient quality, such as age of product (sample oldest lot), liquid products (moisture and pH can degrade vitamins), and effect of light on some nutrients (sample product in transparent packages when appropriate).

- d) Do not sample products that are expired or are within six months of their expiration dates. This will allow sufficient time for analysis and regulatory consideration if the sample is found violative.
- e) Do not collect dietary supplements of herbals, botanicals, or animal extracts, etc. for nutrient analysis **unless** the product also contains a protein, vitamin, or mineral with a label declaration of at least 25% of the RDI or DRV. Refer to [21 CFR 101.9](#) for a list of nutrients and their established RDI or DRV levels.
- f) Each sample must represent a single manufacturing lot code. **Do not commingle lots within a sample.**

### **Microbial USP Analysis**

Collect a sample for microbial USP analysis if the product is suspected of having microbial contamination (*Salmonella* species, *Escherichia coli*, *Staphylococcus aureus* or *Clostridium* species).

- a) [\(2021\)](#) MICROBIAL ENUMERATION TESTS—NUTRITIONAL AND DIETARY SUPPLEMENTS.
- b) [\(2022\)](#) MICROBIOLOGICAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS—NUTRITIONAL AND DIETARY SUPPLEMENTS.
- c) [\(2023\)](#) MICROBIOLOGICAL ATTRIBUTES OF NONSTERILE NUTRITIONAL AND DIETARY SUPPLEMENTS.
- d) Per sample, collect 11 subsamples containing approximately 150 grams/sub-sample. Each sample must represent a single manufacturing lot code.
- e) Analytical lab will be directed by ORS/OFFLO Program Manager.

## E. Sample Collections and Label Examinations (Import)

For products in import status, a sample collection is normally not indicated and referral of the information/documentation to the import field division Compliance Branch (CB) through a labeling examination, including the product label, for articles which appear to be violative. A product label or acceptable copy of a full product label including all sides of the product packaging must be collected for CFSAN to complete a full evaluation of a dietary supplement's label.

### **Label Examinations**

Shipments of dietary supplements being setup for a labeling examination, including the product label, should be prioritized based on the Areas of Emphasis 1-11 above.

### **Sample Collections**

A Compliance sample for Area of Emphasis #3 will consist of 12 retail packages, regardless of size. Collect one retail package from each of 12 randomly selected shipping container or 10% of the number of packages from a single lot, whichever is smaller. Do not commingle lots. In those circumstances where there are not 12 boxes/cases/cartons of a product being offered for

import, then multiple 'retail packages' may be collected from the same shipping container. Under **Reason for Collection** indicate "For <insert Nutrient(s) forming the basis for the claim> analysis."

Sample collections for Microbial USP Analysis, Nutrient Analysis, and Ephedrine Alkaloid Analysis, should follow the directions above in D. Sample Collections (Domestic).

## F. Import Activities

### **Ephedrine Alkaloid-Containing Dietary Supplements (Area of Emphasis #5)**

Dietary supplements containing ephedrine alkaloids are covered by Import Alert [54-13](#) "Detention Without Physical Examination of Dietary Supplements And Bulk Dietary Ingredients Containing Ephedrine Alkaloids From All Countries." A label examination (LEX) will be performed to support regulatory action.

### **Edible Ruminant Products from BSE Affected or At-Risk Countries**

Import Alert [17-04](#) "Detention Without Physical Examination Bulk Shipments of High-Risk Bovine Tissue from BSE-Countries--Bovine Spongiform Encephalopathy" addresses bovine-derived materials intended for human consumption as either finished dietary supplement products or for use as ingredients in dietary supplements.

Be alert for shipments subject to the APHIS prohibition for BSE,

<https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/cattle-disease-information/cattle-bse/cattle-bse>. Refer such entries to the local USDA/APHIS Plant

Protection Quarantine (PPQ) Agriculture Quarantine Inspection Veterinary Medical Officer (AQI VMO); the current list of contacts may be found at:

[https://www.aphis.usda.gov/animal\\_health/downloads/import/aqi-vmo-poc-territory-covered-contact-information.pdf](https://www.aphis.usda.gov/animal_health/downloads/import/aqi-vmo-poc-territory-covered-contact-information.pdf).

### **Dietary Ingredients of Concern**

CFSAN, in conjunction with ORA, will identify potential ingredients of concern through import alerts, directed assignments, and/or guidance, which warrant additional follow-up.

Dietary ingredients of concern include NDIs, ingredients that are not dietary ingredients and pre-DSHEA ingredients that raise safety or other concerns. Ingredients included in [Attachment C](#) should be documented by label examination (LEX) and submitted for regulatory consideration in CMS. Divisions should contact [Dietary Supplements and Labeling Assessment Branch \(DSLAB\)](#) directly for any questions regarding the status of a NDI for use in dietary supplements or dietary supplements containing a dietary ingredient of concern.

### **Dual Language Labels**

Attention should be given to dietary supplement labels which contain the indicated information in one or more languages other than English. Divisions should conduct a label examination to verify the translation accuracy of ingredients and other labeling requirements, particularly regarding declaration of allergens, edible ruminant ingredients, herbal/botanical ingredients, color additives (FD&C Yellow Nos. 5 and 6), and sulfites. If the division does not have a staff member who can translate, please notify the General Program contact person for assistance.

### Dietary Supplements Subject to Import Alerts

Numerous [import alerts](#) are in effect for dietary supplement products or ingredients, including multiple import alerts under the 54 heading (54-##). Import alert [66-41](#), “Detention Without Physical Examination of Unapproved New Drugs Promoted in the U.S.”, may be applicable to dietary supplements and references multiple foreign manufacturers importing dietary supplements found to contain drug ingredients. In addition, import alert [99-39](#), “Detention Without Physical Examination of Imported Food Products appear To Be Misbranded,” may be applicable to dietary supplements.

#### G. Shipping

Divisions are required to coordinate with their servicing lab prior to sample collection. Except for the analyses noted below, please refer to the Laboratory Servicing Table ([LST](#)) to identify an appropriate servicing laboratory. Follow [IOM](#) subchapter 4.5 ‘Sampling: Preparation, Handling, Shipping.’

For samples collected for health claim or nutrient content claim analysis, i.e., Area of Emphasis 3, indicate the suspect nutrient forming the basis for the health claim or nutrient content claim in the **Reason for Collection** section of the collection report.

Microbial USP analysis laboratory should be determined by ORS/OFFLO Program Manager. Samples for Ephedrine Alkaloid Analysis should be directed to [Arkansas Laboratory \(ARKL\)](#) as the primary servicing laboratory, and [Pacific Northwest Laboratory \(PNL\)](#) as the back-up laboratory.

## 2. Reporting

Establishment inspection reports must be completed in eNSpect per [IOM](#) subchapter 5.11.1 ‘Establishment Inspection Report (EIR)’, for all dietary supplement inspections. Each of the ‘Required Elements’ would be covered under separate section headings in the EIR. See [IOM](#) subchapter 8.1 ‘Investigations’ for guidance covering how to conduct and report an investigation.

All corrective actions taken by a firm in response to inspectional observations must be documented in the Corrective Action Reporting (CAR) system, accessible via eNSpect and CMS. Voluntary corrections should be encouraged for all observations and when possible verified prior to the close of the inspection. Use eNSpect to report corrective actions observed during the inspection and those received after the inspection but before the inspection report is finalized in eNSpect. Use CMS to report and assess any corrective actions received after the report has been finalized in eNSpect.

Report resources utilized for sample collection and label examination using the following Program Assignment Codes (PAC) and Problem Area Flags (PAF):

PAC	PAF	PAF Description
21008	NIS	Nutrient Sample Reporting
21008	DIS	Dietary Supplements Analysis (Ephedrine Alkaloid)
21008	MIC	Microbiological Analysis
21008	LEX LBL	Label Examination

## PART IV - ANALYTICAL

### 1. Analyzing Laboratories

Divisions are required to coordinate with their servicing lab prior to sample collection. Please refer to the Laboratory Servicing Table ([LST](#)) for additional guidance. For Ephedrine Alkaloid analysis ARKL is the primary servicing laboratory and PNL is the back-up laboratory. Currently, for Microbiological USP analysis the Analytical lab will be directed by ORS/OFFLO Program Manager.

### 2. Analyses to be Conducted

Nutrient Analysis/Nutrition Sample Reporting (NIS)

Dietary Supplements Analysis (Ephedrine Alkaloid) (DIS)

Dietary Supplement Microbiological Analysis (DSMA)

### 3. Methodology

#### A. Nutrient Analysis

##### 1. Label Review

The label of each sample will be reviewed for conformance with 21 CFR 101.9, 101.36 and other applicable labeling requirements.

##### 2. Analyses

- a) Do not perform nutrient analyses on samples containing more than one manufacturing lot code. Notify the collecting division to re-sample if this occurs.
- b) For compliance samples collected for nutrient analysis in support of an unqualified health claim or nutrient content claim, analyze only for the suspect nutrient.
- c) Otherwise:
  - Select for analysis ONLY those nutrients that are declared as being present at or above 25% of the RDI or DRV.
  - With the above criteria in mind, select a maximum of four (4) nutrients per product, giving first priority to the following nutrients: Vitamin A/Beta Carotene, Selenium, Folic Acid, Pantothenic Acid, Calcium, Potassium, Vitamin C or Vitamin D.
  - For any remaining analysis, select those nutrients declared at the highest percentages of the RDI or DRV at or above 25%. In the case of "ties", randomly select from among the "ties" nutrients for the last selection.
- d) Perform analyses for the selected ingredients as follows:

#### Compliance Samples

Prepare a composite by taking equal portions from each subsample. Use either the "a" or the "b" subsamples. For tablets, capsules, or caplets take a minimum of 2 units per subsample. For other dosage forms, use equal measured amounts from each subsample. The composite should contain an amount of analyte sufficient to perform several determinations. A separate composite shall be prepared by the check analyst for all check analyses. Retain the remaining sub-samples as the 702(b) portion.

### Surveillance Samples

Sample portion for original analysis should be taken from a single subsample. Composite a minimum of 12 servings for tablets, capsules, or bars (e.g., 12 tablets, capsules, bars, etc.) provided that the serving size is 1 tablet, capsule, bar, etc. For liquids or powders, take an appropriately sized (equal to 12 servings) analytical portion from a well-mixed subsample. Another subsample unit will be used for the check analysis if necessary. Additional subsample units will remain intact.

Analyze the composite by methods contained in the AOAC, USP, FDA Foods Program Compendium of Analytical Laboratory Methods, or National Formulary, as applicable and appropriate. Use of methods contained in one of these compendiums must take precedence over use of other methods. If AOAC, USP, or National Formulary methods are not available, then use of an appropriate validated method from the scientific literature or from in-house work is appropriate. Compendial methods must be considered before non-compendial methods are considered.

All methods used whether compendial or non-compendial, must be validated through the use of recovery and reproducibility studies, use of positive and negative controls, use of Standard Reference Material, when available, or in-house quality assurance/quality control materials, etc.

Use of in-house quality assurance/quality control samples is suitable for QA/QC purposes only when adequate documentation of the origin, age, handling (storage procedures), composition, frequency of analysis and results of analysis, etc. is readily available.

- e) For nutrients labeled as USP, the appropriate USP analytical method shall be used for analysis.
- f) Randomly select vitamin or mineral supplements, labeled as meeting USP requirements, for dissolution/disintegration testing using current USP methodology. Priority should be given to calcium supplements then folate/folic acid supplements, and then other appropriate supplements. This testing is not mandatory, and the laboratory should use its discretion in determining when and how many samples to select for dissolution/disintegration testing within the constraints of the available resources.
- g) Perform a check analysis on any sample meeting the conditions outlined in [Part V D. 1. Nutrient Analysis—Conditions of Concern](#). The check analysis should be performed by a second analyst using an official AOAC method, a USP method where designated, or one approved by the Center.

**CAUTION: Do not allow the sample to "age" as many nutrients deteriorate and some minerals precipitate with time.** Vitamins A and C break down when improperly handled. Begin original analysis and check analysis (if necessary) as soon after compositing as possible.

- h) When requested by the Center to support compliance actions, analyze samples labeled with a dietary fiber content using an official AOAC method of appropriate scope (e.g. 985.29, 991.42, 991.43, 993.19, 2017.16).

## B. Ephedrine Alkaloid Analysis

Servicing labs will use either of the following published methods for original analysis of each sample. Additional methods are being developed, and once approved, they may also be used. Each sample should be tested for the six ephedrine alkaloids (EA) included in the methods.

JAOAC Int. 2003 Jul-Aug: 86(4): 657-68; “Determination of Ephedrine Alkaloids in Dietary Supplements and Botanicals by Liquid Chromatography/Tandem Mass Spectrometry: Collaborative Study”. The method may be verified for use in the quantitative determination of each sample and/or confirmation of identity. When possible, it is recommended to determine the concentration of ephedrine alkaloids using liquid chromatography (LC) with tandem mass spectrometry (MS/MS) selective detection as dietary supplements often contain ingredients which interfere with quantification by LC with ultraviolet (UV) detection.

AOAC Official Method 2003.13 Ephedrine Alkaloids in Botanical and Dietary Supplements published as JAOAC Int. 2004 Jan-Feb: 87(1): 1-14; “Determination of Ephedrine Alkaloids in Botanicals and Dietary Supplements by HPLC-UV: Collaborative Study.”

No further evaluation is necessary for samples testing negative by either method. For a sample testing positive, additional analyses are to be conducted, such that the end product is at least a quantitative original analysis, a quantitative check analysis, and an MS confirmation of identity. If an MS confirmation method is also quantitative, it may serve as both the original and check analysis as long as the two analyses are performed by separate analysts.

Analysis of each sample is on a composite basis only, e.g., do not analyze individual tablets or capsules.

Show the calculation and report the concentration ( $\mu\text{g/g}$ ) for individual and total EAs for the composite as directed in the methodology.

Determine the average weight for hard tablets and capsules and the average capsule content weight for soft capsules.

## C. Dietary Supplement Microbial Analysis

Laboratories will use the USP online for the current methodology. See chapters below for specific analytical guidance.

- a. [\(2021\)](#) MICROBIAL ENUMERATION TESTS—NUTRITIONAL AND DIETARY SUPPLEMENTS
- b. [\(2022\)](#) MICROBIOLOGICAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS—NUTRITIONAL AND DIETARY SUPPLEMENTS
- c. [\(2023\)](#) MICROBIOLOGICAL ATTRIBUTES OF NONSTERILE NUTRITIONAL AND DIETARY SUPPLEMENTS

#### 4. Reporting

##### Nutrient Analysis

Use PAC 21008 PAF NIS to report all samples analyzed under this program.

Nutrient Analysis Branch (NAB) in SFFL will report all samples classified as Lab Class 3 based on nutrient analyses to the compliance branch of the collecting division for appropriate regulatory follow-up.

##### Ephedrine Alkaloids

Use PAC 21008 PAF DIS to report the daily dosage level of ephedrine alkaloids found in the product.

Classify samples found to contain any ephedrine alkaloids as Lab Class 3.

Notify the collecting division and the CFSAN Program Contact of samples that are classified as Lab Class 3 as soon as the original, check, and confirmation analysis are complete, and the laboratory supervisor has cleared the worksheet. Promptly report positive and negative findings into FACTS.

##### Microbial USP Analysis

Use PAC 21008 PAF MIC to report all samples analyzed under this program.

Classify samples based on the guidance in [\(2023\)](#) Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements.

Notify the collecting division, CFSAN Program Contact and ORS Program Contact of samples that are classified as Lab Class 2/3 as soon as the analyses are completed in FACTS.

## PART V - REGULATORY/ADMINISTRATIVE STRATEGY

### 1. Findings

The goal of this regulatory and administrative strategy is to obtain high rates of industry compliance with the dietary supplement CGMP regulations under [21 CFR Part 111](#), and labeling requirements under [21 CFR Part 101](#), and other applicable laws (including those relating to new dietary ingredients and other ingredients) and to gain prompt voluntary correction of deficiencies. Regulatory recommendations such as Warning Letters or Untitled Letters must be submitted to CFSAN Division of Enforcement via electronic copy (e.g., MS word, pdf files, other electronic documents, etc.) through proper supervisory channels when significant GMP observations are found and documented, when potentially unlawful ingredients are identified, and/or when significant labeling deviations exists, including health fraud with inappropriate claims being made for products. However, as appropriate, swift enforcement action will be taken when significant problems present a threat to public health. If a division determines that there is a direct threat to public health during an inspection, such as a shipment of dietary supplement found to be positive for pathogens or containing undeclared allergens, the division should immediately contact [CFSAN/OC and OEIO](#) to discuss enforcement options. Refer to [Attachment B](#) for standard language on significant violations.

### 2. Actions

**Please note that all reasonable steps should be taken to obtain voluntary compliance prior to initiating regulatory action.** If the facility's response is inadequate to protect public health, all available administrative and legal tools should be considered, such as a regulatory meeting, untitled letter, warning letter, administrative detention, registration suspension, mandatory recall, seizure, or injunction. If the division feels that administrative or legal action is warranted (with the exception of regulatory meeting, untitled letter, or warning letter), management should initiate a preliminary assessment call with CFSAN Office of Compliance Division of Enforcement (DE). Refer to the Regulatory Procedures Manual (RPM) for more information; [Chapter 4 - Advisory Actions](#); [Chapter 5- Administrative Actions](#); and [Chapter 6- Judicial Actions](#).

#### A. Administrative and Legal Actions for Imminent Public Health Hazards

##### **FDA-Requested Recall or Mandatory Recall Order**

Although unusual in the absence of demonstrating specific product contamination, an FDA-requested recall could be considered in urgent situations and based on a Class I health hazard evaluation. Refer to RPM [Chapter 7- Recall Procedures](#) for more information. If a determination is made that there is reasonable probability that an article of food is adulterated under section 402 of the FD&C Act or misbranded under section 403(w) of the FD&C Act and the use or exposure to such article will cause a serious adverse health consequences or death to humans or animals (SAHCODHA) and the firm refuses to take voluntary corrective actions, including recall, after FDA request, mandatory recall under section 423 may be warranted.

##### **Administrative Detention**

If a determination is made that there is reason to believe that an article of food is adulterated or misbranded, administrative detention under section 304 of the FD&C Act may be considered to prevent the movement of such food while the FDA prepares for additional action (e.g. seizure, injunction).

### **Seizure/ Injunction**

When the facility's response to the Warning Letter does not adequately address direct or indirect risks, if violations are sufficiently egregious and/or persistent, and/or if the facility refuses to conduct a voluntary recall, a seizure and/or injunction should be considered.

### **Suspension of Food Facility Registration**

If a facility registered under section 415(a) manufactures, processes, packs, receives, or holds food that has a reasonable probability of causing SAHCODHA; and that facility created, caused or was otherwise responsible for that reasonable probability of SAHCODHA; or knew of, or had reason to know of, the reasonable probability of SAHCODHA, and packed, received, or held such food, suspension of food facility registration may be considered. If warranted, the state should be engaged to determine if state enforcement actions such as embargo or permit revocation can be utilized to stop production or the movement of product while FDA is considering enforcement actions.

## **B. Compliance Activities**

The following should be used in recommending an appropriate regulatory action to CFSAN/DE:

### **GMP Violations**

#### Manufacturers of dietary supplements:

- Failure to establish and follow written quality control review procedures or significant quality control procedures not implemented.
- Lack of written master manufacturing records or elements of the MMR not included.
- Failure to establish finished product specification release criteria. Failure to test all or a subset of finished batches to ensure the batch meets finished product specification release criteria.
- Failure to establish component specifications for dietary ingredients or failure to conduct identity testing.
- Failure to use appropriate and scientifically valid methods to test components or finished products.
- No written batch records or significant elements not included in batch records.
- Significant physical plant or equipment deficiencies.

#### Distributors of dietary supplements:

- Failure to establish and follow written procedures for quality control including procedures for release of packaged and labeled dietary supplements.

- Failure to establish and ensure packaging and labeling specifications are met.
- Failure to establish and follow written procedures for holding and distributing operations.
- Failure to establish and follow written procedures for packaging and/or labeling operations; and manufacturing and batching records pertaining to these operations.
- Failure to establish and follow written procedures for product complaints.
- Failure to establish and follow written procedures for returned dietary supplements.

### **Label Violations**

Division compliance branches should refer to the references provided in Part VI when evaluating labels under the Areas of Emphasis listed below. FDA's website includes a [dietary supplement labeling guide](#) that includes additional information for use in evaluating labels. Refer to [Attachment B](#) for standard language to be included in Warning Letters.

### DOMESTIC PRODUCTS

#### Areas of Emphasis Nos. 6, 10, and 11

OHAFO CB may consider issuing Warning Letters directly to firms whose product(s):

- 1) Fail to bear nutrition information under 21 CFR 101.36 and are not exempt; or
- 2) Are in solid oral dosage form and contain added iron or iron salts but do not bear the mandatory warning statement.

This direct reference authority applies only to product labels that fall into statements (1) and/or (2) above but conform to all the other areas of emphasis including providing mandatory labeling information. Regulatory recommendations against product labels that do not conform to one of the other areas of emphasis must be handled as indicated under Regulatory/Administrative Strategy.

ODSP must be included on the distribution list for these letters. A copy of these direct reference Warning Letters must be uploaded into the CMS case file.

#### Areas of Emphasis 1, 2, 3, 5, 6, 7, 8, 9 and 10

Divisions should prepare Warning Letter recommendations against firms whose product(s):

- Fail to bear statement of identity on the principal display panel, i.e., use of the term "dietary supplement" or "[\*] supplement" with the blank [\*] filled in with the name of the dietary ingredient or a term appropriately descriptive of dietary ingredients in the product.
- Bear (a) a health claim or a nutrient content claim that has not been authorized by FDA; (b) a health claim that is not the subject of a letter granting enforcement discretion in response to the court decision in Pearson vs. Shalala; (c) a nutrient content claim that is not appropriately based on an authoritative statement as provided for in section 403(r)(2)(6) of the Act; (d) or any health claim that appears to be based on an authoritative statement under the Food and Drug Administration

Modernization Act (FDAMA). At this time, the Act does not provide for the use of health claims based on authoritative statements in the labeling of dietary supplements.

- Bear egregious disease claims or structure/function claims that may be unsubstantiated. Products that bear inappropriate disease claims or that appear to bear egregiously false or misleading structure/function claims should be referred to CFSAN for evaluation.
- Bear nutrition labeling (“Supplement Facts” label) with missing elements of 101.36 including significant format deviations under 21 CFR 101.36(e).
- Uses the term “ginseng” to describe the product or an ingredient and the product or ingredient is not an herb or herbal ingredient derived from a plant classified within the genus “Panax.”
- Fail to disclose a required major food allergen.
- Fail to bear other mandatory nutrition labeling.

### **Nutrient Analysis**

#### 1. Conditions of Concern

- The analysis supports the fact that the product does not qualify to make the health claim or nutrient content claim contained on the product label (Area of Emphasis No. 4), or
- The sample does not comply with the requirement found at 21 CFR 101.9(g)(4) regarding nutrients that are not present in the declared amounts.

This same threshold applies when recommending regulatory action against products labeled as meeting a USP monograph.

Generally, for products that do not qualify to make a certain health claim or nutrient content claim, the recommendation would be accompanied by supporting analytical results. However, there may be instances where a deviation in this area may be supportable based solely on label review without related analytical results.

#### 2. Applicable Charges for Regulatory Actions

The appropriate charge(s) for the above types of deviations would be:

- 403(a)(1) (false and misleading labeling) for products that do not qualify for a health claim or nutrient content claim on the product label.
- 403(a)(1) (false and misleading labeling) and also 402(b)(1) (adulteration; valuable constituent has been in whole or in part omitted...) for products that do not comply with 21 CFR 101.9(g)(4). These are the charges to be included in all regulatory actions involving nutrient deficiencies recommended under this program.
- 403(r)(1) (nutrient content claims) if the product includes a nutrient content or health claims and the product does not meet the nutrient requirements to make

the claim, based on the analytical results.

### **Adverse Event Reporting Requirements**

Section 761 of the Act applies to the requirements for adverse event supplements. Firms are required by statute to submit to FDA all reports of serious adverse events associated with dietary supplements that they receive. FDA expects responsible persons to perform follow up investigations of those serious adverse events reported to them to obtain at least the minimum five data elements needed to make a submission to FDA. FDA stated in the [Guidance for Industry](#) that it does not intend to pursue enforcement action against firms who make diligent efforts to follow-up but are unsuccessful in obtaining the minimum information needed to make a submission. In addition, the statute requires that firms make and keep records of all adverse events reported to them for 6 years, regardless of whether the adverse event is reported to FDA.

If you find that a firm has failed to perform any or all of these requirements, the division should submit a Warning Letter recommendation. If the firm has performed the requirements but the documentation or actions appear to be inadequate, the division may consider submitting an Untitled Letter recommendation.

### **Ephedrine Alkaloid Containing Dietary Supplements**

The Center is prepared to move forward quickly against dietary supplement products determined by analytical testing to contain ephedrine alkaloids. Voluntary actions by the responsible firms (e.g., destruction of existing inventory and commitment to comply with the law and regulations) are an acceptable and efficient alternative to enforcement action that still achieves compliance and removes adulterated product from the market. Where possible, voluntary action should be publicized in order to provide appropriate deterrence to other firms.

In the absence of voluntary actions, compliance branches should discuss the findings with the CFSAN Compliance/Enforcement contact. If appropriate, divisions should submit seizure recommendations through CMS.

Refer to Section 6-1 of the RPM for additional guidance on submitting seizure recommendations. The recommendation package should include the worksheet for the positive findings, legible digital copies of product labels, and all supporting documentation.

Follow-up source/supplier for raw materials:

Division Compliance Branches must request trace back investigation of finished product and suppliers for any product that tests positive for ephedrine alkaloids. If the product or raw material is of import origin, submit the relevant information on country, port of entry, shipper, importer, etc. to ORA Division of Import Operations (DIO) ICB through CMS as an import alert recommendation.

### **Products Containing Edible Ruminant Tissue or Tissue-Derived Ingredients from BSE Affected or At-Risk Countries**

Bovine-derived ingredients cannot be used in dietary supplements if they adulterate the product under any provision of Section 402 of the Act.

If evidence of any one of the following situations is collected in a firm, the division must forward the EIR and all documentation through CMS to CFSA for further regulatory consideration.

1. A bovine-derived ingredient is a prohibited cattle material under 21 CFR 189.5(a) if it is a specified risk material that has not been inspected and passed for human consumption by a competent authority or is otherwise a prohibited material under 21 CFR 189.5(a). Affirmative evidence of the use of prohibited cattle material must be collected.
2. If the firm is using bovine-derived ingredients, they must have records to show that the food is not manufactured from, processed with, or does not otherwise contain prohibited cattle materials (21 CFR 189.5(c)). Documentation of the lack of these records must be collected.
3. Under the dietary supplement CGMP regulations, firms must establish specifications for animal-derived ingredients that are necessary to ensure the quality of the dietary supplement. Firms must also take necessary actions to determine that specifications are met. If such specifications are not established or met, collect adequate documentation of the deficiency.

### **Products Containing Identified Ingredients of Concern**

Regulatory action against dietary supplements that contain ingredients that may be unlawful for any reason, including new dietary ingredients that have not complied with the requirements in section 413 of the Act, ingredients that are not dietary ingredients, ingredients that are unsafe food additives, and ingredients that raise safety concerns, are a priority for the Center. Please consult with ODSP to determine whether action against an ingredient will be supported and what the appropriate charge(s) should be.

#### **C. Imports**

When imported products identified as dietary supplements or as dietary supplement ingredients appear to be non-compliant based on FDA statute/regulation, based on label examination, sample collection and/or are subject to detention without physical examination (DWPE), divisions should consider detaining the entry per the established process.

In addition, for those violative firms and products not already subject to DWPE for the indicated violation, the Division should submit a recommendation for DWPE to ORA DIO's Import Compliance Branch (ICB), as appropriate, via CMS. Divisions should follow the criteria outlined in the [RPM Chapter 9 - Import Operations and Actions](#), Subchapter for Detention without Physical Examination when recommending firms and/or products for addition DWPE under the appropriate Import Alert. An original or quality copy of the label **MUST** be included in the package submitted to the ORA DIO ICB for review, along with other relevant evidence to support the violation.

#### D. Additional Information

Voluntary correction by a firm is often the most effective and expedient means to obtain compliance and to protect public health. Divisions should take steps to obtain voluntary correction prior to initiating regulatory action. When voluntary correction is not forthcoming, pursue routine regulatory procedures to address significant observations. Refer to [FMD-86 Establishment Inspection Report Conclusions and Decisions](#) for further guidance.

If a facility inspected under this program has a Class I recall and/or conditions are observed that represent a significant public health concern, a conference call between the division Compliance Branch, and CFSAN/OC and ORA/OHAFO program contacts identified in [part VI](#) of this program should be scheduled before closing the inspection to discuss possible enforcement strategies. If this information is known prior to beginning the inspection, a call should be scheduled prior to the start of the inspection.

The division should submit any recommendation for enforcement follow-up through CMS. If CFSAN feels an inspection classified as VAI should be classified as OAI, a request will be made to the division to provide the full narrative EIR and exhibits through CMS for review. If subsequently an OAI reclassification is suggested by CFSAN, a meeting will be scheduled between the divisions and CFSAN/OC and OEIO.

### 3. Regulatory Follow-Up

To verify the implementation of corrective actions, divisions should conduct follow-up inspections within **6 months** of the compliance action being finalized for facilities with inspection classifications of **OAI** and that were observed to have significant CGMP deficiencies, and/or unauthorized health claims according to [FMD-86](#) and [RPM Chapter 4](#). **If there are significant deficiencies or a risk to public health, then follow-up must be conducted as soon as possible after the close of the inspection and completion of compliance action.** Follow-up inspections may include the collection of product samples at the division's discretion.

Prior to initiating the re-inspection, divisions should hold an enforcement strategy discussion with CFSAN OC, ORA OHAFO program contacts, and state partners to discuss potential follow-up actions if the firm continues to have significant violations. If the follow-up inspection reveals that the firm continues to have conditions that are likely to lead to the adulteration and misbranding of dietary supplements, the division should consider more severe enforcement action based on these repeat offenses. Divisions should initiate a call with CFSAN OC, CFSAN ODSP, and ORA OHAFO program contacts when an inspection revealed significant repeat observations. [FDA Contacts for Regulatory Partners](#).

Facilities with an inspection classification of NAI and VAI should be re-inspected at the frequency designated in the Food Safety Modernization Act (FSMA) for high risk and non-high-risk facilities.

#### Nutrient Analysis

### Compliance Samples

If the domestic sample was collected as required in 21 CFR 101.36(f)(1) and a lot size suitable for seizure is available, recommend a seizure. If the domestic sample does not fully comply with the requirements of 21 CFR 101.36(f)(1) or if a lot size suitable for seizure is not available, recommend issuance of a Warning Letter.

### Surveillance Samples

Warning Letter recommendations should be prepared and forwarded for surveillance samples meeting the criteria in V. B. Label Violations above.

### Import Samples

For import samples that fail to bear nutrition labeling, submit an import alert recommendation for addition of the responsible firm and product to DWPE to ORA's DIO/ICB through CMS.

Each recommendation must include a copy of the available entry documents, the collection report (if the recommendation is based on sample collection), an original product label (or quality copy), all analyst worksheets (if the recommendation is based on sample collection), and other pertinent information, such as documentation of method performance for all "Non-Official" methods utilized.

## PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

### 1. References

Major guidance and reference materials pertaining to this program are listed below. Additional guidance may be found in the [resource library](#).

- A. [Investigations Operations Manual \(IOM\)](#)
- B. [Regulatory Procedures Manual \(RPM\)](#)
- C. [FDA Food Labeling Guide](#)
- D. [FDA Dietary Supplement Label Guide](#)
- E. [United States Pharmacopeia \(USP\)](#)

#### For Areas of Emphasis

- No. 1 – Products that make disease and/or drug claims - Sections 301(d), 505(a) and 502(f)(1) of the FD&C Act.
- No. 2 – Products that contain new dietary ingredients without the required notification - Sections 402(f) and/or 413 of the FD&C Act, [Dietary Supplement Ingredient Advisory List](#) and [Attachment C](#).
- No. 3 – Products that bear health claims or nutrient content claims--See 21 CFR 101.13 and 101.14, section 403(r)(1)(A) and 403(r)(1)(B), [FDA Food Labeling Guide](#), [Qualified Nutrient Content Claims](#), and [Qualified Health Claims](#).
- No. 4 – Failure to maintain records for cattle derived material--See [21 CFR 189.5](#).
- No. 5 – Products that appear to contain a source of ephedrine alkaloids--See [21 CFR 119.1](#), section 402(1)(a)(A) of the Act, and [Attachment C](#).
- No. 6 – Products bearing significant “Supplement Facts” label deviations--See 21 CFR 101.36, section 403(q)(5)(F) and [Chapter IV of the Dietary Supplement Labeling Guide](#). Products that fail to bear an appropriate statement of identity--See 21 CFR 101.3(g), section 403(s)(2)(B) and [Small Entity Compliance Guide: Statement of Identity, Nutrition Labeling and Ingredient Labeling of Dietary Supplements](#).
- No. 7 – Products that fail to declare a major food allergen--See Section 403(w) of the Act and the [Food Allergen Labeling and Consumer Protection Act of 2004](#).
- No. 8 – Products labeled with “Siberian ginseng”--See Section 403(u) of the Act and 21 CFR 101.4(h).
- No. 9 – Products that fail to bear other mandatory labeling information--See [Dietary Supplement Labeling Guide](#).
- No.10 – Products bearing significant “Supplement Facts” label deviations--See 21 CFR 101.36, section 403(q)(5)(F) of the Act and [Chapter IV of the Dietary Supplement Labeling Guide](#).
- No.11 – See 21 CFR 101.17(e)(1), section 403(a)(1) of the Act and [Small Entity Compliance Guide: Label Warning Statements for Iron-Containing Supplements and Drugs](#)

## 2. Attachments

- A. Exemptions from Nutrition Labeling (“Supplement Facts” Label)
- B. Standard Language for Warning Letters
- C. List of Ingredients of Concern for Coverage During Inspections and Field Exams
- D. Guidance on Evidence Development and Documentation to Support Regulatory Action
- E. CGMP Requirements Applicable to Operations Performed by Firm

## 3. Program Contacts

### CFSAN

Purpose	Name	Organization	Contact
General Program Guidance	<a href="#">Joshua Adams</a>	CFSAN/DFPG/PAMB	312-596-4166
Enforcement Guidance	<a href="#">Quyên Tien</a>	CFSAN/OC/DE	215-717-3705
Technical Information	<a href="#">Haijing Hu</a>	CFSAN/ODSP	301-796-6555
Technical Information	<a href="#">rTAN</a>	CFSAN/ODSP	See <a href="#">part II(2)(F)</a>

### ORA

Purpose	Name	Organization	Contact
Domestic/Foreign Guidance National Expert	<a href="#">Justin Boyd</a>	ORA/OHAFO	608-264-5332x106
Domestic/Foreign Guidance Program Expert	<a href="#">Lourdes Andujar</a>	ORA/OHAFO/DDHAFO	787-238-0114
Import Guidance	<a href="#">Robert Hatch</a>	OEIO/DIO/IOB	240-402-6081
Technical Information	<a href="#">Zachary Miller</a> (Micro) <a href="#">Yanxuan (Tina) Cai</a> (Chemistry)	ORS/OFFLO	303-236-9694 240-402-1369
Technical Information	<a href="#">rTAN</a>	ORA/OHAFO	See <a href="#">part II(2)(F)</a>

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## PART VII - CENTER RESPONSIBILITIES

The Office of Dietary Supplement Programs will provide subject matter expertise in the maintenance and evaluation of the Compliance Program and provide guidance to the Office of Compliance with regard to program priorities, relevant evaluation questions, and recommended program changes. The Office of Compliance will lead the effort and work in conjunction with the Office of Dietary Supplement Programs to prepare routine compliance program evaluations. Evaluation will be conducted on a periodic basis and outline the program office's current objectives, general and specific program evaluation questions, list recommendations for process improvement, and highlight data patterns and trends for better targeting and resource allocation. The Office of Compliance will make these evaluations available as well as FSMA Tracker reports that can be run annually or as frequently as needed to track accomplishments. Instructions on how to access these reports are available at:

<http://inside.fda.gov:9003/ProgramsInitiatives/Food/FieldPrograms/ucm015369.htm>

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Food/FieldPrograms/UCM609042.pdf>

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**ATTACHMENT A – EXEMPTIONS FROM NUTRITION LABELING ("SUPPLEMENT FACTS" LABEL)**

A dietary supplement is not required to have a "Supplement Facts" label if it is:

- a. Offered for sale by a small business that has not more than \$50,000 gross sales per year from food sales or no more than \$500,000 from total sales in accordance with 21 CFR 101.36(h)(1).
- b. A low-volume product (i.e., less than 100,000 units sold annually) sold by a firm with less than 100 full-time equivalent employees in accordance with 21 CFR 101.36(h)(2) and for which a claim for exemption has been filed annually with CFSAN Office of Nutrition and Food Labeling (ONFL).
- c. Shipped in bulk form, not distributed to consumers in such form, and used in the manufacture of other dietary supplements in accordance with 21 CFR 101.36(h)(3).

NOTE: The exemptions for small businesses and low-volume products are available only to products whose labels bear no claims or other nutrition information.

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**ATTACHMENT B – STANDARD LANGUAGE FOR WARNING LETTERS IN AREAS OF EMPHASIS**

Follow the format in [Chapter 4 - Advisory Actions](#) of the current edition of the Regulatory Procedures Manual (RPM). This is not an all-inclusive list, as appropriate, specimen charges for both domestic and import cases that may be applicable to this program include:

**Dietary Supplement Health Fraud (New and Misbranded drug violations under section 505(a) and 502(f)(1)):**

- Your product(s) is/are not generally recognized as safe and effective for the above-referenced uses and, therefore, the product(s) is/are “new drugs” under section 201(p)(1) of the Act [21 U.S.C. 321(p)(1)]. New drugs may not be legally introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in sections 301(d) and 505(a) of the Act [21 U.S.C. 331(d), 355(a)]. FDA approves a new drug on the basis of scientific data submitted by a drug sponsor to demonstrate the drug is safe and effective.
- A drug is misbranded under section 502(f)(1) of the Act [21 U.S.C. 352(f)(1)] if the drug fails to bear adequate directions for its intended use(s). “Adequate directions for use” means directions under which a layperson can use a drug safely and for the purposes for which it is intended (21 CFR 201.5). Prescription drugs, as defined in section 503(b)(1)(A) of the Act [21 U.S.C. 353(b)(1)(A)], can only be used safely at the direction, and under the supervision, of a licensed practitioner. Your product(s) is/are intended for treatment of one or more diseases that are not amenable to self-diagnosis or treatment. Therefore, it is impossible to write adequate directions for a layperson to use this product safely for its intended purposes. Accordingly, your product(s) fail/fails to bear adequate directions for its intended use and, therefore, the product(s) is/are misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. The introduction or delivery for introduction into interstate commerce of this misbranded drug violates section 301(a) of the Act [21 U.S.C. § 331(a)].

**Adulterated Dietary Supplement:**

- Your dietary supplement product(s) is/are adulterated within the meaning of section 402(g)(1) of the Act [21 U.S.C. § 342(g)(1)] because the products have been prepared, packed, or held under conditions that do not meet the Current Good Manufacturing Practice (CGMP) regulation for dietary supplements (21 CFR Part 111).
- Your product(s) is/are adulterated within the meaning of section 402(f)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 342(f)(1)(A)(i)] because it is a dietary supplement that presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling.
- Your product(s) is/are adulterated under sections 402(f)(1)(B) and 413(a) of the Act [21 U.S.C. §§ 342(f)(1)(B) and 350b(a)] because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.
- Your product(s) is/are adulterated under section 402(f)(1)(A) of the Act because it contains ephedrine alkaloids that cause the product to present an unreasonable risk of illness or injury

under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use (21 CFR 119.1).

- The product is adulterated under section 402(a)(4) of the Act because it was manufactured from, processed with, or otherwise contains material from cattle and the firm does not have records sufficient to demonstrate that the food is not manufactured from, processed with, or does not otherwise contain, prohibited cattle materials. 21 CFR 189.5(d).
- Your product(s) is/are adulterated under section 402(a)(1) [21 U.S.C. § 342(a)(1)] of the Act, because they bear or contains a poisonous or deleterious substance which may render them injurious to health. [pathogens or heavy metal contaminants identified from analytical results and/or OOS reports].
- Your [insert product] is adulterated under section 402(a)(2)(C)(i) of the Act [21 U.S.C. § 342(a)(2)(C)(i)] because it contains [non-dietary ingredient], an unsafe food additive under section 409(a) of the Act [21 U.S.C. § 348(a)]. If a substance added to food is not generally recognized as safe (GRAS) by qualified experts for its intended use in food and does not qualify for any of the other exemptions from the food additive definition, it is a food additive.<sup>2</sup> Food additives require premarket approval based on data demonstrating safety. Any food additive that has not been approved for its intended use in food is deemed to be unsafe and causes the food to be adulterated under section 402(a)(2)(C)(i) of the Act [21 U.S.C. § 342(a)(C)(i)].
  - The definition of “food additive” in section 201(s) of the Act [21 U.S.C § 321(s)] does not include dietary ingredients used in dietary supplements as defined in section 201(ff)(1) of the Act [21 U.S.C § 321(ff)(1)] or substances that are GRAS under the conditions of intended use. [Name of ingredient] does not qualify as a dietary ingredient under section 201(ff)(1) of the Act [21 U.S.C. § 321(ff)(1)] because it is not a vitamin, mineral, amino acid, herb or other botanical, dietary substance for use by man to supplement the diet by increasing the total dietary intake, or concentrate, metabolite, constituent, extract, or combination of any of the preceding dietary ingredient types. Neither is [name of ingredient] GRAS under its conditions of use in your dietary supplement product. Because [name of ingredient] does not qualify as a dietary ingredient and is not GRAS or otherwise exempt from the food additive definition, your [name of the product] is adulterated under section 402(a)(2)(C)(i) of the Act because they contain an unsafe food additive. The introduction or delivery for introduction into interstate commerce of any food that is adulterated is a prohibited act under section 301(a) of the Act [21 U.S.C. § 331(a)].<sup>3</sup>
- The term “dietary supplement” is defined in section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(ff)]. Given that you have declared [Insert new dietary ingredient (NDI) previously reviewed and cleared by CFSAN] as a dietary ingredient in the labeling of your product, we assume you have a basis to conclude that [insert NDI] is a “dietary ingredient” under section 201(ff)(1) of the Act [21 U.S.C. § 321(ff)(1)]. If you have a basis to conclude that [insert NDI] is a “dietary ingredient,” it would also be a “new dietary ingredient” (i.e., a dietary ingredient not marketed in the United States before October 15, 1994) under section 413(d) of the Act [21 U.S.C. § 350b(d)].

Under section 413 of the Act [21 U.S.C. § 350b], a dietary supplement that contains a new dietary ingredient shall be deemed adulterated under section 402(f) of the Act [21 U.S.C. § 342(f)] unless it meets one of two requirements:

- a. The dietary supplement contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or
- b. There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

To the best of FDA's knowledge, there is no information demonstrating that [Insert NDI] was lawfully marketed as a dietary ingredient in the United States before October 15, 1994, nor is there information demonstrating that this ingredient has been present in the food supply as an article used for human food in a form in which the food has not been chemically altered.

Assuming [Insert NDI] is a dietary ingredient, in the absence of such information, [Insert NDI] would be subject to the notification requirement in section 413(a)(2) of the Act [21 U.S.C. § 350b(a)(2)] and 21 CFR 190.6. Products for which the manufacturer or distributor is required to submit a new dietary ingredients notification under section 413(a)(2) and 21 CFR 190.6, but for which the required notification has not been submitted, are adulterated under sections 402(f) and 413(a) of the Act [21 U.S.C. §§ 342(f) and 350b(a)].

- Even if a new dietary ingredient notification had been submitted under section 413(a)(2) and 21 CFR 190.6, we know of no evidence that would establish that [Insert NDI] could be lawfully marketed as a new dietary ingredient in your [Name of Product] product. In the absence of a history of use or other evidence of safety establishing that [Insert NDI], when used under the conditions recommended or suggested in the labeling as a dietary ingredient, will reasonably be expected to be safe, dietary supplements containing [Insert NDI] as a new dietary ingredient are adulterated under sections 402(f) and 413(a) of the Act because there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under sections 301(a) and (v) of the Act [21 U.S.C. § 331(a) and (v)]. To the best of FDA's knowledge, there is no history of use or other evidence of safety establishing that [Insert NDI] will reasonably be expected to be safe when used as a dietary ingredient.

### **Misbranded Dietary Supplement:**

- Your product is misbranded within the meaning of section 403(q)(5)(F) of the Act in that the label fails to bear nutrition labeling ("Supplement Facts" label), which is required under 21 CFR 101.36, and is not exempt from this requirement.
- Your product is misbranded within the meaning of sections 403(i)(1) and 403(s)(2)(B) of the Act in that the label fails to identify the product using the term dietary supplement (21 CFR 101.3(g)).
- Your product is misbranded within the meaning of section 403(r)(1)(A)/(B) of the Act in that the label bears the nutrient content claim/health claim "\_\_\_," which has not been authorized by FDA regulation or on the basis of an authoritative statement under section 403(r)(2)(G) or 403(r)(3)(C) of the Act, or has not been the subject of a letter granting enforcement discretion in response to the Pearson vs. Shalala court decision.
- Your product is misbranded within the meaning of sections 403(a)(1) and 201(n) of the Act in that the label, labeling, or display of the product with added iron, fails to bear the required warning statement (21 CFR 101.17(e)).
- Your product is misbranded within the meaning of section 403(u) of the Act in that it purports to be or is represented as ginseng, but it is not an herb or herbal ingredient derived from a plant classified within the genus *Panax*.
- Your product is misbranded within the meaning of section 403(w) of the Act [21 U.S.C. 343 (w)] in that the label fails to declare all major food allergens present in those products, as required by section 403(w)(1). Section 201(qq) of the Act [21 U.S.C. 321(qq)] defines a major food allergen as milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soybeans, as well as any food ingredient that contains protein derived from one of these foods, with the exception of highly refined oils. A food is misbranded if it is not a raw agricultural commodity and it is, or it contains an ingredient that bears or contains, a major food allergen, unless either:
  - The word "Contains," followed by the name of the food source from which the major food allergen is derived, is printed immediately after or adjacent to the list of ingredient, [section 403(w)(1)(A) of the Act, 21 U.S.C. 343(w)(1)(A)]; or
  - The common or usual name of the major food allergen in the list of ingredients is followed in parentheses by the name of the food source from which the major food allergen is derived, except that the name of the food source is not required when either the common or usual name of the food source appears elsewhere in the ingredient list (unless the name of the food source that appears elsewhere in the ingredient list appears as part of the name of an ingredient that is not a major food allergen) [section 403(w)(1)(B) of the Act, 21 U.S.C. 343(w)(1)(B)].
- For tree nuts, fish, or crustacean shellfish, the term "name of the food sources from which the major food allergen is derived" means the name of the specific type of nut or species of fish or Crustacean shellfish [section 403(w)(2), 21 U.S.C. 343(w)(2)].
- Your product is misbranded within the meaning of section 403(q)(1)(A) of the Act [21 U.S.C. § 343(q)(1)(A)] because the product label fails to include a serving size in accordance with 21 CFR 101.36(b). The terms "serving" or "serving size" for a dietary supplement are defined in 21 CFR 101.9(b) and 21 CFR 101.12(b) Table 2, as the maximum amount recommended on the label for consumption per eating occasion.

- Your product is misbranded within the meaning of section 403(y) of the Act [21 U.S.C. § 343(y)] in that the label fails to bear a domestic address or domestic phone number through which the responsible person (as described in section 761) may receive a report of a serious adverse event with such dietary supplements. Specifically, each product label does not include a complete domestic address or domestic phone number.
- Your product is misbranded within the meaning of section 403(i)(2) of the Act [21 U.S.C. § 343(i)(2)] in that the product label fails to declare the common or usual names of each ingredient used as required by 21 CFR 101.36 and 21 CFR 101.4.
- Your product is misbranded within the meaning of section 403(e)(2) of the Act [21 U.S.C. § 343(e)(2)] because the label fails to accurately declare the net quantity of contents on the principal display panel as required by 21 CFR 101.7 and 15 U.S.C. § 1453(a)(2) of the Fair Packaging and Labeling Act.
- Your product is misbranded under section 403(e)(1) [21 U.S.C. § 343(e)(1)] of the Act in that the labels fail to declare the place of business, including the ZIP code, in accordance with 21 CFR 101.5.
- Your product is misbranded within the meaning of section 403(s)(2)(C) of the Act [21 U.S.C. § 343(s)(2)(C)] because the label fails to identify the part of the plant (e.g., root, leaves) from which each botanical dietary ingredient in the product is derived, as required by 21 CFR 101.4(h)(1).
- Under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(ff)(1)], a dietary ingredient is a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances. [Name of non-dietary ingredient] is not a vitamin, a mineral, an herb or other botanical, or an amino acid. In addition, according to our research, [name of non-dietary ingredient] is not a dietary substance for use by man to supplement the diet by increasing the total dietary intake. Finally, [name of non-dietary ingredient] is not a concentrate, metabolite, constituent, extract, or combination of a vitamin; mineral; herb or other botanical; amino acid; or dietary substance for use by man to supplement the diet by increasing the total dietary intake. Accordingly, [name of non-dietary ingredient] is not a dietary ingredient within the definition set forth in section 201(ff)(1) of the Act. Declaring [non-dietary ingredient] in your product labeling as a dietary ingredient causes your products marketed as dietary supplements to be misbranded under section 403(a)(1) of the Act [21 U.S.C. § 343(a)(1)] in that the labeling is false or misleading in any particular.

## **Area of Emphases**

### Area of Emphasis No. 1

Products that bear disease claims on the labels or labeling and offered for sale:

The product is not generally recognized as safe and effective for the above-referenced uses and, therefore, it is a “new drug” under section 201(p)(1) of the Act [21 U.S.C. 321(p)(1)]. New drugs may not be legally introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in sections 301(d) and 505(a) of the Act [21 U.S.C. 331(d), 355(a)]. FDA

approves a new drug on the basis of scientific data submitted by a drug sponsor to demonstrate the drug is safe and effective.

A drug is misbranded under section 502(f)(1) of the Act [21 U.S.C. 352(f)(1)] if the drug fails to bear adequate directions for its intended use(s). “Adequate directions for use” means directions under which a layperson can use a drug safely and for the purposes for which it is intended (21 CFR 201.5). Prescription drugs, as defined in section 503(b)(1)(A) of the Act [21 U.S.C. 353(b)(1)(A)], can only be used safely at the direction, and under the supervision, of a licensed practitioner. The product is intended for treatment of one or more diseases that are not amenable to self-diagnosis or treatment. Therefore, it is impossible to write adequate directions for a layperson to use this product safely for its intended purposes. Accordingly, the product fails to bear adequate directions for its intended use and, therefore, the product(s) is/are misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. The introduction or delivery for introduction into interstate commerce of this misbranded drug violates section 301(a) of the Act [21 U.S.C. § 331(a)].

#### Area of Emphasis No. 2

The product is adulterated under sections 402(f)(1)(B) and 413(a) of the Act [21 U.S.C. §§ 342(f)(1)(B) and 350b(a)] because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

#### Area of Emphasis No. 3

The product is misbranded within the meaning of section 403(r)(1)(A)/(B) of the Act in that the label bears the nutrient content claim/health claim “ ,” which has not been authorized by FDA regulation or on the basis of an authoritative statement under section 403(r)(2)(G) or 403(r)(3)(C) of the Act, or has not been the subject of a letter granting enforcement discretion in response to the Pearson vs. Shalala court decision.

#### Area of Emphasis No. 4

The product is adulterated under section 402(a)(3) of the Act because it was manufactured from, processed with, or otherwise contains material from cattle and the firm does not have records sufficient to demonstrate that the food is not manufactured from, processed with, or does not otherwise contain, prohibited cattle materials. 21 CFR 189.5(d).

#### Area of Emphasis No. 5

The product is adulterated under section 402(f)(1)(A) of the Act because it contains ephedrine alkaloids that cause the product to present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use (21 CFR 119.1).

#### Area of Emphasis No. 6

The product is misbranded within the meaning of sections 403(i)(1) and 403(s)(2)(B) of the Act in that the label fails to identify the product using the term dietary supplement (21 CFR 101.3(g)).

Failure to bear an appropriate statement of identity on the principal display panel, i.e., use of the term "dietary supplement" or "supplement", with the blank filled in with the name of the dietary ingredient or a term appropriately descriptive of dietary ingredients in the product:

The product is misbranded within the meaning of 403(s)(2)(B) of the Act [21 U.S.C. § 343 (s)(2)(B)] because it does not include a statement of identity as a “dietary supplement” as required by 21 CFR 101.3(g).

#### Area of Emphasis No. 7

The product is misbranded within the meaning of section 403(w) of the Act [21 U.S.C. 343 (w)] in that the label fails to declare all major food allergens present in those products, as required by section 403(w)(1). Section 201(qq) of the Act [21 U.S.C. 321(qq)] defines a major food allergen as milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soybeans, as well as any food ingredient that contains protein derived from one of these foods, with the exception of highly refined oils. A food is misbranded if it is not a raw agricultural commodity and it is, or it contains an ingredient that bears or contains, a major food allergen, unless either:

- 1.The word “Contains,” followed by the name of the food source from which the major food allergen is derived, is printed immediately after or adjacent to the list of ingredient, [section 403(w)(1)(A) of the Act, 21 U.S.C. 343(w)(1)(A)]; or
- 2.The common or usual name of the major food allergen in the list of ingredients is followed in parentheses by the name of the food source from which the major food allergen is derived, except that the name of the food source is not required when either the common or usual name of the food source appears elsewhere in the ingredient list (unless the name of the food source that appears elsewhere in the ingredient list appears as part of the name of an ingredient that is not a major food allergen) [section 403(w)(1)(B) of the Act, 21 U.S.C. 343(w)(1)(B)].

For tree nuts, fish, or crustacean shellfish, the term “name of the food sources from which the major food allergen is derived” means the name of the specific type of nut or species of fish or Crustacean shellfish [section 403(w)(2), 21 U.S.C. 343(w)(2)].

Guidance on the allergen labeling requirements in section 403(w) may be found on FDA’s website at [www.fda.gov](http://www.fda.gov).

Specifically, your product [name of product] is misbranded under section 403(w) in that the product fails to declare the major food allergen [name of major allergen], which is a [dietary ingredient] [subcomponent of the dietary ingredient x], as specified by the Act.

#### Area of Emphasis No. 8

The product is misbranded within the meaning of section 403(u) of the Act in that it purports to be or is represented as ginseng, but it is not an herb or herbal ingredient derived from a plant classified within the genus *Panax*.

#### Area of Emphasis No. 9

The following are examples of the types of deviations that could fall under this area. It is not intended to be a comprehensive list of labeling deviations in this Area of Emphasis.

##### **Failure to bear net weight:**

The product is misbranded under section 403(e)(2) of the Act because the label fails to bear the net quantity of contents.

##### **Failure to bear domestic address or domestic phone number on product:**

The product is misbranded within the meaning of section 403(y) of the Act [21 U.S.C. § 343(y)] because the label fails to include a domestic address or domestic phone number through which the responsible person (as described in section 761) may receive a report of a serious adverse event with such dietary supplements. “Domestic address or domestic phone number” means a complete address or phone number.

##### **Failure to bear name and place of business of manufacturer or packer:**

The product is misbranded under section 403(e)(1) of the Act because the label does not bear the name and place of business of the manufacturer, packer, or distributor.

#### Area of Emphasis No. 10

The product is misbranded within the meaning of section 403(q)(5)(F) of the Act in that the label fails to bear nutrition labeling (“Supplement Facts” label), which is required under 21 CFR 101.36, and is not exempt from this requirement.

#### Area of Emphasis No. 11

The product is misbranded within the meaning of sections 403(a)(1) and 201(n) of the Act in that the label, labeling, or display of the product with added iron, fails to bear the required warning statement (21 CFR 101.17(e)).

**ATTACHMENT C – LIST OF INGREDIENTS OF CONCERN FOR COVERAGE DURING INSPECTIONS**

NDIs that require notification (and never been submitted)			
<i>Ingredient</i>	<i>Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
DMBA	<ul style="list-style-type: none"> <li>• 1,3-Dimethylbutylamine</li> <li>• 2-Amino-4-Methylpentane Citrate</li> <li>• 4-Amino-2-Methylpentane Citrate</li> <li>• 4-Amino Methylpentane Citrate</li> <li>• Amperall</li> <li>• 4-AMP Citrate</li> <li>• 4-Methyl-2-Pentanamine</li> </ul>	402(f)(1)(B)	<p>a constituent derived from <i>Camellia sinensis</i> tea leaves</p> <p><a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/dmba-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/dmba-dietary-supplements</a></p>
Acacia rigidula	<ul style="list-style-type: none"> <li>• A. rigidula</li> <li>• Vachellia rigidula</li> <li>• Chaparro Prieto</li> <li>• Blackbrush</li> </ul>	402(f)(1)(B)	<p>support memo includes the botanical or extract of the botanical</p> <p><a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/acacia-rigidula-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/acacia-rigidula-dietary-supplements</a></p>
Hordenine	<ul style="list-style-type: none"> <li>• 4-[2-(Dimethylamino)ethyl]phenol</li> <li>• N,N-dimethyltyramine</li> <li>• p-hydroxy-N,N-dimethylphenethylamine</li> <li>• 2-(4-hydroxyphenyl)N,N-dimethyl-ethylamine</li> <li>• anhaline</li> <li>• eremursine</li> <li>• cactine</li> <li>• peyocactine</li> </ul>	402(f)(1)(B)	<p>a constituent of several botanicals including cactus, barley (<i>Hordeum vulgare</i>), <i>Aconitum tanguticum</i> (Maxim.) Stapf, seaweeds, <i>Senecio scandens</i>, <i>Coryphantha ramillosa</i>, and bitter orange (<i>Citrus Aurantium</i>).</p>

NDIs that require notification (and never been submitted)			
<i>Ingredient</i>	<i>Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
Higenamine	<ul style="list-style-type: none"> <li>• Norcoclaurine</li> <li>• Demethylcoclaurine</li> <li>• O-Demethylcoclaurine</li> <li>• (R)-Higenamine</li> <li>• 6,7-dihydroxy-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline</li> <li>• Coclaurine, O-demethyl-, (±)-</li> <li>• 6,7-Isoquinolinediol, 1,2,3,4-tetrahydro-1-((4-hydroxyphenyl)methyl)-,</li> </ul>	402(f)(1)(B)	a constituent of botanicals, such as <i>Aconitum</i> root, <i>Tinospora crispa</i> stems, <i>Nandina domestica</i> Thunberg fruit, <i>Gnetum parvifolium</i> lianas, and <i>Nelumbo nucifera</i> embryo and leaves.
Octopamine	<ul style="list-style-type: none"> <li>• alpha-(Aminoethyl)-4-hydroxybenzenemethanol</li> <li>• alpha-(Aminoethyl)-p-hydroxybenzyl alcohol</li> <li>• alpha-Aminoethyl-4-hydroxybenzylalkohol</li> <li>• Analet</li> <li>• Benzenemethanol, alpha-(aminomethyl)-4-hydroxy-</li> <li>• Norden</li> <li>• Norfen</li> <li>• Norphen</li> <li>• Norsympathol</li> <li>• Norsympatol</li> <li>• Norsynephrine</li> <li>• Octapamine</li> <li>• Octopamina</li> <li>• Octopaminum</li> <li>• p-Hydroxyphenylethanolamine</li> <li>• p-Norsynephrin</li> <li>• Paraoxyphenyl aminoethanol</li> <li>• WV 562-Isooctyl amine</li> <li>• 1-(p-Hydroxyphenyl)-2-aminoethanol</li> </ul>	402(f)(1)(B)	a constituent of botanical isolated from the leaves and juice of the Meyer lemon ( <i>Citrus</i> spp.) and from bitter orange ( <i>Citrus aurantium</i> ).

NDIs that require notification (and never been submitted)			
<i>Ingredient</i>	<i>Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
Cesium chloride	<ul style="list-style-type: none"> <li>• Cesium chloride</li> <li>• Cesium monochloride</li> <li>• Dicesium dichloride</li> <li>• EC 231-600-2</li> <li>• EINECS 231-600-2</li> <li>• HSDB 7149</li> <li>• NSC 15198</li> <li>• Tricesium trichloride</li> <li>• UNII-GNR9HML8BA</li> </ul>	402(f)(1)(B)	<a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/public-health-alert-concerning-dietary-supplements-containing-cesium-salts">https://www.fda.gov/food/dietary-supplement-products-ingredients/public-health-alert-concerning-dietary-supplements-containing-cesium-salts</a>

Unsafe Food Additive			
<i>Ingredient</i>	<i>Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
DMAA	<ul style="list-style-type: none"> <li>• 1,3-DMAA</li> <li>• 1,3-Dimethylamylamine</li> <li>• 1,3-Dimethylpentylamine</li> <li>• 2-Amino-4-methylhexane</li> <li>• 2-Hexanamine, 4-methyl- (9CI)</li> <li>• 4-Methyl-2-hexanamine</li> <li>• 4-Methyl-2-hexylamine</li> <li>• Dimethylamylamine</li> <li>• Geranamine</li> <li>• Methylhexanamine</li> <li>• Methylhexanenamine</li> <li>• Pelargonium graveolens extract</li> <li>• Geranium extract</li> </ul>	402(a)(2)(C)(i)	<a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/dmaa-products-marketed-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/dmaa-products-marketed-dietary-supplements</a>

Unsafe Food Additive			
<i>Ingredient</i>	<i>• Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
DMHA	<ul style="list-style-type: none"> <li>• 1,5-Dimethylhexylamine</li> <li>• 1,5-DMHA</li> <li>• 2-amino-5-methylheptane</li> <li>• 2-amino-6-methylheptane</li> <li>• 2-aminoisoheptane</li> <li>• 2-Heptylamine, 6-methyl-</li> <li>• 2-Isooctyl amine</li> <li>• 2-Metil-6-amino-eptano</li> <li>• 6-Amino-2-methylheptane</li> <li>• Amidrine</li> <li>• Octodrine</li> <li>• Vaporpac</li> </ul>	402(a)(2)(C)(i)	
Tianeptine	<ul style="list-style-type: none"> <li>• Tianeptine sulfate</li> <li>• Tianeptine sodium powder</li> <li>• Tianaa</li> <li>• Tianna Green</li> <li>• Tianna Red</li> <li>• Tianna White</li> </ul>	402(a)(2)(C)(i)	

## Ingredients that do not meet the definition of a dietary ingredient

<b><i>Ingredient</i></b>	<b><i>Ingredient Synonyms</i></b>	<b><i>Charge Applicable</i></b>	Comments
BMPEA	<ul style="list-style-type: none"> <li>• <math>\beta</math>MePEA</li> <li>• R-beta-methylphenethylamine</li> <li>• R-beta-methylphenethylamine HCl</li> <li>• Beta-methylphenethylamine</li> <li>• <math>\beta</math>-methylphenylethylamine</li> <li>• 1-amino-2-phenylpropane</li> <li>• 2-phenylpropan-1-amine</li> <li>• 2-phenylpropylamine</li> <li>• alpha-benzylethylamine</li> <li>• 1-phenyl-1-methyl-2-aminoethane</li> <li>• beta-methylbenzeneethanamine</li> <li>• beta-phenylpropylamine</li> <li>• 2-phenyl-1-propanamine</li> </ul>	403(a)(1)	<p>Was often marketed as a constituent of <i>Acacia rigidula</i> but it is not actually a constituent of this botanical</p> <p><a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/bmpea-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/bmpea-dietary-supplements</a></p>
Methylsynephrine	<ul style="list-style-type: none"> <li>• oxilofrine</li> <li>• p-hydroxyephedrine</li> </ul>	403(a)(1)	<p>Was often marketed as a constituent of bitter orange (<i>Citrus aurantium</i>) but it is not actually a constituent of this botanical</p> <p><a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/methylsynephrine-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/methylsynephrine-dietary-supplements</a></p>

Ingredients that do not meet the definition of a dietary ingredient			
<i>Ingredient</i>	<i>Ingredient Synonyms</i>	<i>Charge Applicable</i>	Comments
Phenibut	<ul style="list-style-type: none"> <li>• fenibut</li> <li>• phenigam</li> <li>• PhGaba</li> <li>• Phenigamma</li> <li>• Phenygam</li> <li>• 4-Amino-3-phenylbutanoic acid</li> <li>• <math>\beta</math>-(aminomethyl)benzenepropanoic acid</li> <li>• beta-(Aminomethyl)hydrocinnamic acid</li> <li>• <math>\beta</math>-phenyl-<math>\gamma</math>-aminobutyric acid</li> </ul>	403(a)(1)	<a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/phenibut-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/phenibut-dietary-supplements</a>
Picamilon	<ul style="list-style-type: none"> <li>• pikatropin</li> <li>• pikamilon</li> <li>• nicotinyl-gamma-aminobutyric acid</li> <li>• nicotinyl-GABA</li> </ul>	403(a)(1)	<a href="https://www.fda.gov/food/dietary-supplement-products-ingredients/picamilon-dietary-supplements">https://www.fda.gov/food/dietary-supplement-products-ingredients/picamilon-dietary-supplements</a>

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**ATTACHMENT D – GUIDANCE ON EVIDENCE DEVELOPMENT AND  
DOCUMENTATION TO SUPPORT REGULATORY ACTION**

- CPG Sec. 440.100 Marketed New Drugs Without Approved NDAs and ANDAs (See link: <https://www.fda.gov/media/72007/download>)
- CPG Sec 120.500 Health Fraud - Factors in Considering Regulatory Action (See link: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-120500-health-fraud-factors-considering-regulatory-action>)
- IOM (See link: <https://www.fda.gov/media/113432/download> (Chapter 2- see 2.7 Detention Activities, 2.7.1.3.2 Food, 2.7.1.3.6 Drug, 4.3.8.3 Labeling), Chapter 5- See 5.5.5.5 Drug/Dietary Supplement Status
- CPG Sec 100.250 Food Facility Registration- Human and Animal Food (See link: <https://www.fda.gov/media/88691/download>)
- Guidance for Industry and FDA Staff: Questions and Answers Regarding Mandatory Food Recalls (See link: <https://www.fda.gov/media/117429/download>)

**ATTACHMENT E – CGMP REQUIREMENTS APPLICABLE TO OPERATIONS  
PERFORMED BY FIRM**

1. Labeling Review – Evaluate the product labels, printed promotional materials, and online presence including websites and social media for the use of disease claims that would make the products unapproved new drugs. Verify labels comply with the nutrition labeling (“Supplement Facts” label), adverse event reporting requirements, allergen labeling, and other applicable labeling requirements.
2. Requirements of Quality Control – Review procedures for the responsibilities of quality control and ensure quality control personnel conduct required activities. Verify that Quality Control has complied with the following requirements:
  - a. Establish and follow written procedures for the responsibility of the quality control operations.
  - b. Identify the personnel responsible for quality control operations and their qualifications.
  - c. Approval of procedures for manufacturing and the procedures are followed.
  - d. Approval of master manufacturing records and batch records for applicable operation at the firm.
  - e. Approval of specifications the firm has for components, in process materials, labels, packaging, and finished products.
  - f. Determine if QC personnel reviewed and approved all laboratory control processes associated with the production and process control system, if applicable.
  - g. Review firm’s documentation to ensure appropriate tests or exams are used to for components and finished products testing.
  - h. Assess the firm’s disposition decision for approval of components, packaging, labels, in-process and finished product specifications.
  - i. Review the results of the firm’s qualification of the supplier of the components, and review Certificates of Analysis for the incoming materials.
  - j. Review test result to make disposition determination on components, packaging, labels, in-process and finished products.
  - k. Review adequacy of corrective actions.
3. Quality Indicators – Review recalls, quality complaint investigations, adverse events, laboratory out-of-specification (OOS) investigations, and deviation investigations.
  - a. Evaluate testing and examination methods to ensure they are scientifically valid. Evaluate the reference standards and the characterization process of the reference standards if firm develops in-house reference standards.
  - b. Review if laboratory record reflects the analytical results used to support disposition decisions.
  - c. Evaluate the record keeping for laboratory operations.

4. Facility and Equipment – Conduct a walkthrough inspection of areas where components or finished dietary supplements are exposed to the environment and evaluate the sanitation and maintenance of the facility and equipment. Evaluate the potential for contamination, allergen cross-contact, and pests. Determine the adequacy of employee hygiene.
  - a. Assess the water quality when water is a component of the dietary supplement.
  - b. Assess calibration of equipment for manufacturing, including automated, mechanical or electronic equipment used in manufacturing, packaging etc.
  - c. Assess the firm’s controls established for equipment (including software on a computer controlled process) and if changes are approved by QC personnel and instituted only by authorized personnel.
  - d. Request and review firm’s written procedures for cleaning, sanitizing (if necessary), and maintenance of all equipment and utensils and contact surfaces, and are they followed?
  - e. Request and review established written procedures and assess the firm’s control of the holding and distributing space for components, finished product, reserved samples, etc.
  
5. Product Review –
  - a. Master Manufacturing Record – Review the master manufacturing record and determine whether it contains required information and identifies appropriate specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement.
  - b. Batch Production Record – Review the executed batch record and determine whether it contains required information and documents specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement are met. Review batch records and determine if they received adequate review to make a decision to release or reject the batch for distribution. Evaluate if personnel engaged in production activities are following written procedures for manufacturing operations.
  - c. Components – Review at least three components used in the product to ensure appropriate specifications have been established. Review testing data or documentation showing component specifications are met. Determine whether methods used to verify specifications are appropriate and scientifically valid. Evaluate that precautionary measures are being used to prevent contamination of components of dietary supplements.
  - d. Finished Dietary Supplement – Ensure appropriate finished dietary supplement specifications have been established. Review testing data or documentation showing finished dietary supplement specifications are met. Determine whether methods used to verify specifications are appropriate and scientifically valid. Evaluate that rejected dietary supplements have been properly quarantined and dispositioned.
  - e. Manufacturing, Packaging, and Labeling Operations - includes procedures, processes, and control of the packaging and labeling operations for dietary supplement products. It includes written procedures for packaging and labeling, packaging and labeling process, visual inspection of package and labeling, control for the use of packages and labeling, label specifications, label reconciliations.

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- i. Review MMR and BPR and observe manufacturing, packaging and labeling operations.
  - ii. Confirm that packaging and label used meet the established specifications
  - iii. Evaluate that labels received have been properly reviewed and released by QC personnel and that required lot traceability procedures are being used.
  - iv. Evaluate that rejected packaging and labels have been properly quarantined and dispositioned.