COMPLIANCE PROGRAM

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

SUBJECT:	DIETARY SUPPLEMENTS – FOREIGN AND DOMESTIC INSPECTIONS, SAMPLING, AND IMPORTS	
IMPLEMENTATION DATE:	9/30/2024	
PRODUCT CODES:	All Human Food Dietary Supplements **Class Code: Select appropriate code** **Industry Code: 54** **Subclass Code: B, C, and Y only** **PIC Code: Select appropriate code**	
PRODUCT/ASSIGNMENT CODES (PACs):	21008	all sample collection and analysis
	21008F	all full scope inspections of dietary supplement manufacturers under 21 CFR part 111
	21008D	all inspections of dietary supplement facilities responsible for introducing their own brand of finished products into commerce under 21 CFR part 111
	21008W	all inspections of dietary supplement warehouse facilities under 21 CFR part 111
	21008P	all inspections of dietary supplement packaging/labeling facilities under 21 CFR part 111
	21R829	all activities involving nutritional health fraud – human food

FIELD REPORTING REQUIREMENTS:

The Office of Inspections and Investigations (OII) 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 OII established timeframes. The OII 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 OII and the Human Foods Program (HFP).

OII 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 HFP's Office of Compliance Enforcement (OCE), for evaluation through CMS in accordance with Regulatory Procedures Manual (RPM) timeframes.[1]

During an inspection, if you obtain information pertaining to inadequate notification of mandatory reporting requirements (e.g., reporting of serious adverse events[2], FDA notification of New Dietary Ingredients[3], FDA notification of structure/function claims[4]) 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 OII divisions should use this revised compliance program for all sample collections and CGMP inspections satisfying the statutory obligation for inspections of dietary supplement manufacturers.

[1] For further information see Part V Regulatory/Administrative Strategy
[2] Federal Food, Drug and Cosmetic Act (FD&C Act), § 761
[3] FD&C Act, § 413
[4] FD&C Act, § 403(r)(6)

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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) that is labeled as dietary supplement, intended for ingestion, and is 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 in 2019, 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) in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements final rule was published on June 25, 2007. 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) 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 compliance with CGMP to ensure that 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.

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 comply with the requirements of the FD&C Act.
- To enforce dietary supplement regulations for products that do not comply with the FD&C Act 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 for firms that manufacture dietary supplements.
- Distributor Inspection – will cover compliance with the applicable CGMP requirements for firms that are ultimately responsible for introducing or causing introduction of the firm's brand of finished dietary supplements into interstate commerce. Distributors are the responsible party listed on product labeling and must ensure that finished product on the market is not misbranded or adulterated.
- Warehouse Inspection – will cover compliance with the applicable CGMP requirements for firms that hold, and possibly distribute dietary supplements, but do not perform manufacturing, packaging, or labeling operations.
- Packaging/Labeling Inspection – will cover compliance with the applicable CGMP requirements for firms that solely perform packaging and/or labeling operations.

HFP 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 OII divisions. This list will identify the likely scope of inspection under dietary supplement CGMP for each facility (e.g., full scope manufacturer, distributor, warehouse, package/label), when possible. The division should change the scope of inspection based on the type of operations performed by the firm.

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 HFP.

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), (2) and (3): contains at least one dietary ingredient, intended to be ingested, and labeled as a dietary supplement. Since this label determination can be fact-

dependent and other 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 Information on Select Dietary Supplement Ingredients and Other Substances. 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

Dietary supplement FY workplan will assign all firms as PAC 21008F, Full Scope Inspections. Depending on the dietary supplement operations being performed the appropriate dietary supplement PAC should be utilized by the Investigator conducting 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 the OCE to determine whether collection of samples for the surveillance purpose is appropriate.

(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.

Table 1 –Reporting PACs

Reporting PAC	Description
21008	Dietary Supplement Sample Collection and Analysis (all examinations and sample collections)
21008F	Dietary Supplement Full Scope Inspections at Manufacturers under 21 CFR 111
21008D	Dietary Supplement Inspections of Distributors under 21 CFR 111
21008W	Dietary Supplement Inspections of Warehouse Facilities under 21 CFR 111
21008P	Dietary Supplement Inspections of sole Packaging/Labeling Facilities under 21 CFR 111
21R829	All Activities involving Health Fraud – Human Food

Table 2 – Planning PACs

Planning PAC	Description
21008	Dietary Supplement Sample Collection and Analysis
21008F	Dietary Supplement Full Scope Inspections at Manufacturers under 21 CFR 111

Table 3 – Operation Codes

Operation Type	Operation Code
Inspection	11 (foreign) / 12 (domestic)
Investigation	15 (foreign) / 13 (domestic)
Remote Regulatory Assessment	19 (foreign) / 16 (domestic)
Sample Collection	33 (import) / 31 (domestic)
Sample Analysis	43 (import) / 41 (domestic)
Label/Document Review	52 (import) / 51 (domestic)
Field Exam	53

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 CPs. Use the appropriate PAC when reporting sample collections under this compliance program:

- Domestic Acidified and Low-Acid Canned Foods, 7303.070
- Domestic and Import Food Additives and Color Additives, 7309.006
- Foreign Supplier Verification Programs Inspections, 7303.878
- Juice HACCP Inspection Program, 7303.847

- Medical Foods – Import and Domestic, 7321.002
- Mycotoxins in Domestic and Imported Foods, 7307.001
- Pesticides and Industrial Chemicals in Domestic and Imported Foods, 7304.004
- Preventive Controls and Sanitary Human Food Operations 7303.040
- Seafood Processor, Products, and Importer Inspection Program, 7303.842
- Toxic Elements in Food & Foodware and Radionuclides in Food – Import and Domestic, 7304.019
- 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 foodfacilityregistration@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.

(3) Foreign Authorities

Follow OII Division of Foreign Food Investigations and Global Operations (DFFIGO) procedures and IOM section 5.7.3.7.2 when foreign competent authorities are present during FDA foreign inspections or investigations.

F. When to Contact Other Offices within the FDA

For technical assistance regarding dietary supplements, please contact dsTANWorkgroup@fda.hhs.gov. If the question(s) is related to an ongoing inspection or investigation, please include "ONGOING EI" as the prefix in the subject line in addition to the firm name and FEI if possible. If the question(s) is related to a product covered by additional commodity-specific regulations (e.g., acidified, seafood, juice) include appropriate

SMEs and OII National Experts on the email to dsTANWorkgroup@fda.hhs.gov.

Dietary supplements are exempt from the preventive control requirements in Subparts C & G of 21 CFR part 117, so most questions regarding dietary supplements would be directed to the dietary supplement email address dsTANWorkgroup@fda.hhs.gov. You may also copy SMEs on the rTAN list. However, there are circumstances when it is appropriate to send questions that may be related to dietary supplements to the PCHF regulator technical assistance network (rTAN), which can be reached at rTANWorkgroup@fda.hhs.gov. These circumstances include:

- Field inspection staff are not sure if a product is a conventional food covered under 21 CFR 117 or a dietary supplement covered under 21 CFR 111.
- Field inspection staff are inspecting/preparing to inspect a dietary ingredient facility which would be covered under 21 CFR 117.
- Field inspection staff are not sure if a product is a dietary ingredient manufacturer covered under 21 CFR 117 or a dietary supplement manufacturer covered under 21 CFR 111.

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.

A list of rTAN commodity-specific SMEs, OII National Expert SMEs, and lead program contacts (rTAN list) can be found in the resource library or open-access DS SharePoint site.

G. Resource Instructions

- Resources for sample collections, analyses, import field/label exams, and emerging issues for dietary supplements are provided in the OII 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**. 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)

The appropriate PAC should be used based on the firm's operations and the inspectional approach(es) utilized during a dietary supplement inspection. The only dietary supplement PAC that can be used in combination with other dietary supplement PACs during an inspection is Distributor Inspection PAC 21008D. The 'Required Elements' should be documented for each dietary supplement PAC that is utilized during an inspection. Please reference Attachment E – PAC Usage Decision Tree for an infographic on determining which PAC should be used during an inspection.

Manufacturing Inspections

Manufacturing inspections will be conducted at firms that conduct some or all of the manufacturing steps for a dietary supplement, and will cover compliance with all CGMP requirements, **Full Scope Manufacturing Inspections.**
Full Scope manufacturing inspection coverage includes all required elements listed below, see Attachment D for additional details 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. Collection of finished product labels, in their original state (this does not include label proofs, or label specifications), should be collected for every product covered during the inspection. If the original label is not available at the manufacturer, reasonable measures should be taken to collect evidence of how the finished product will be labeled in its final form. Determine if distributor operations are occurring at this site. If so, then the distributor PAC 21008D will be used in addition to PAC 21008F and document the Distributor

inspection required elements. Evidence for 483 items should include the pervasiveness of an issue if it can be documented.

Required Elements

1. **Online Labeling Review:** Evaluate the firm's website, social media, and any other online presence for the use of disease claims which would make the products unapproved new drugs, potential misbranded labeling, ingredients of concern identified in the Select Dietary Supplement Ingredient Directory, Active Pharmaceutical Ingredients (APIs), and New Dietary Ingredients (NDIs). Capture screenshots with the website and date/time clearly visible on the image which will be included as attachments in the EIR.

   Disease Claim References – 21 CFR 101.93(g)(2)(i) – (x)
   Misbranding –21 CR 101.36(a) – (j), and 21 CFR 101.9
   Allergen Cross Contamination/Declaration/Warning Statements: Sections 201(qq) and 403(w) of the FD&C Act; 21 CFR part 117 subpart B; Guidance for Industry; Compliance Policy Guide 555.250
   Iron Warning Statement: 101.17(e) – Solid Oral Dosage Form
   Active Pharmaceutical Ingredients - Dietary Supplement Ingredient Directory, Orange Book
   New Dietary Ingredients - NDI Database
   Adverse Event Reporting Requirements- Guidance for Industry
   Structure Function Claims- 21 CFR 101.93(b) – (f), Structure/Function Claims
   - **Structure Function Claim Disclaimer** – 21 CFR 101.93(b)

2. **On-Site Label Review:** Evaluate at least 3 product labels (this may or may not include products that were reviewed as part of the online labeling review). This review will cover nutrition labeling, adverse event reporting requirements, structure function and disease claims, the inclusion of a structure function disclaimer, allergen labeling, and other applicable labeling requirements. This information along with the online labeling review must be captured and documented in the EIR, specifically in the Labeling Observation Table.
3. **Requirements of Quality Control**: Review written procedures for the responsibilities of quality control and ensure quality control personnel conduct required activities. Such activities may include, but are not limited to, review of written procedures, specifications, testing, and processes; conducting material reviews and making disposition decisions as necessary; review and approval of calibration; releasing components, packaging, and labeling from quarantine; approving or rejecting any treatment or in-process adjustment; reviewing and approving all master manufacturing records, and batch production records; reviewing and approving any reprocessing, repackaging or relabeling; and reviewing and approving all return and complaint operations.
4. **Quality Indicators**: Review recall operations performed by the firm; complaint investigations, including adverse events; laboratory out-of-specification (OOS) investigations; deviation investigations initiated after an unanticipated occurrence,

or a deviation from the master manufacturing record; and returned product investigations.

5. **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. Review written procedures for holding and distribution and related records.
6. **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 executed batch records 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. Dietary Ingredients and Components – Review all dietary ingredient specifications and testing/examination methods and results (dietary ingredients are raw materials listed inside the dietary Supplement Facts label) for the finished products followed during the inspection. If the finished product contains a large number of ingredients, such as in a multivitamin, a minimum of seven ingredient specifications should be covered based on the ingredient risk potential. When possible, vary ingredients selected to cover mineral/vitamin, botanical/enzyme, and protein/(probiotic/prebiotic). Review at least three component specifications and testing/examination methods and results (components are materials listed in the "Other Ingredients" section of the label such as excipients) for the finished products followed during the inspection. Ensure appropriate scientifically valid specifications have been established and appropriate scientifically valid testing/examination methods have been performed to ensure specifications are met. Determine whether methods used to verify specifications are also appropriate and scientifically valid.
   d. Packaging and Labeling – Review at least two specifications for packaging components and/or label specifications and associated testing/examination methods performed on these materials.
   e. Finished Dietary Supplement – Ensure appropriate finished dietary supplement specifications have been established. Review testing/examination 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 firm's brand of finished dietary supplements into interstate commerce. This includes firms that may choose to warehouse products or at firms that do not hold or physically distribute products. Distributors are the responsible party listed on product labeling in accordance with 21 CFR 101.5(a)-(e) and must ensure that finished product on the market is not misbranded or adulterated. If possible, at least three finished dietary supplement products should be included in the product review; if three finished products are not available, review the number of finished products available. Collection of finished product labels, in their original state (this does not include label proofs, or label specifications), should be collected for every product covered during the inspection. All required elements applicable to the distributor's operations should be covered.

If the distributor is warehousing and distributing products, then PAC 21008W will be used in addition to PAC 21008D. If the distributor does not warehouse or physically distribute products from a location such as an office, then PAC 21008D will be the only PAC used. If the distributor is conducting manufacturing activities such as blending and encapsulating, then PAC 21008F will be used in conjunction with PAC 21008D. If the distributor is conducting packaging and/or labeling operations, then PAC 21008P will be used in addition to PAC 21008D. Refer to the required elements for each applicable inspection type pertinent to the firm's operations.

Required Elements

1. **Online Labeling Review:** Evaluate the firm's website, social media, and any other online presence for the use of disease claims which would make the products unapproved new drugs, potential misbranded labeling, ingredients of concern identified in the Select Dietary Supplement Ingredient Directory, Active Pharmaceutical Ingredients (APIs), and New Dietary Ingredients (NDIs). Capture screenshots with the website and date/time clearly visible on the image which will be included as attachments in the EIR.

   Disease Claim References – 21 CFR 101.93(g)(2)(i) – (x)
   Misbranding –21 CR 101.36(a) – (j), and 21 CFR 101.9
   Allergen Declaration/Warning Statements: Sections 201(qq) and 403(w) of the FD&C Act; Guidance for Industry
   Iron Warning Statement: 101.17(e) – Solid Oral Dosage Form
   Active Pharmaceutical Ingredients - Dietary Supplement Ingredient Directory, Orange Book
   New Dietary Ingredients - NDI Database
   Adverse Event Reporting Requirements- Guidance for Industry
   Structure Function Claims- 21 CFR 101.93(b) – (f), Structure/Function Claims
   - **Structure Function Claim Disclaimer** – 21 CFR 101.93(b)

2. **On-Site Label Review:** Evaluate at least 3 product labels (this may or may not include products that were reviewed as part of the online labeling review). This review will cover nutrition labeling, adverse event reporting requirements, structure function and disease claims, the inclusion of a structure function disclaimer, allergen labeling, and other applicable labeling requirements. This information along with the online labeling review must be captured and documented in the EIR, specifically in the Labeling Observation Table.
3. **Responsibility:** Identify/confirm who is the most responsible individual at the firm, who controls the website and label content, who created and controls the formulation(s), who are the firm's contract manufacturer(s) - including the name, address, FEI's, and any related quality agreements. This information must be collected for products associated with the online labeling review and the on-site label review. Document who is responsible for holding reserve samples.
4. **Complaints and Returns:** Determine how the firm reviews product complaints and review any written procedures for handling complaints, adverse events, and product returns. Review the investigations performed by quality control for complaints received along with any related disposition decisions. Review the firm's complaint log, along with complaints received by FDA, to ensure that all requirements of Subpart O are being followed. Determine if serious adverse events were reported to FDA. Document how the firm handles product returns, including salvaging, reprocessing, or treating returned products, to ensure that all requirements of Subpart N are being followed.

Warehouse Inspections

Warehouse inspections will be conducted at all firms that hold and/or fulfill dietary supplements, but do not perform manufacturing, packaging, or labeling. These firms may distribute their own brand of dietary supplement products, as well as dietary supplement products owned by someone else. All required elements applicable to the operations must be covered. If a distributor is also warehousing, then PAC 21008D will be used in addition to PAC 21008W and document the Distributor inspection required elements.

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. Verify written sanitation procedures were established.
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.

Packaging and Labeling Inspections

Packaging and Labeling inspections will be conducted at firms that solely conduct packaging, labeling, re-packaging, and/or relabeling operations. A Manufacturing inspection must be conducted for firm's that conduct any other manufacturing steps (such as blending, tableting, encapsulating) for a dietary supplement and will utilize PAC 21008F. 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. Collection of finished product labels, in their original state (this does not include label proofs, or label specifications), should be collected for every product covered during the inspection.

Determine if distributor operations occur at this site. If so, then the distributor PAC 21008D will be used in addition to PAC 21008P and document the Distributor inspection required elements. Evidence for 483 items should include the pervasiveness of an issue if it can be documented.

Required Elements

1. **Requirements of Quality Control:** Review written procedures for the responsibilities of quality control and ensure quality control personnel conduct required activities. Such activities may include, review of written procedures, specifications, testing, and processes; conducting material reviews and making disposition decisions as necessary; review and approval of calibration; releasing bulk supplement products, packaging, and labeling from quarantine; approving or rejecting any treatment or in-process adjustment; reviewing and approving all master manufacturing records, and batch production records; reviewing and approving any reprocessing, repackaging or relabeling; and reviewing and approving all return and complaint operations.
2. **Quality Indicators:** Review recall operations performed by the firm; complaint investigations, including adverse events; laboratory out-of-specification (OOS) investigations; deviation investigations initiated after an unanticipated occurrence, or a deviation from the master manufacturing record; and returned product investigations.
3. **Facility and Equipment:** Conduct a walkthrough inspection of areas where bulk materials 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. Review written procedures for holding and distribution and related records.

4. 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.

c. Bulk Dietary Supplements – Review bulk supplement specifications and testing/examination methods and results which must provide sufficient assurance that the product received is adequately identified and is consistent with the purchase order. Ensure appropriate scientifically valid specifications have been established and appropriate scientifically valid testing and/or examination methods have been performed to ensure specifications are met.

d. Packaging and Labeling – Review at least two specifications for packaging components and/or label specifications and associated testing/examination methods performed on these materials.

Adverse Event Reporting

Human Foods Complaint System (HFCS) 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 HFP 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.

Dietary Supplements Containing Ephedrine Alkaloids

1) If the product label states that it contains "ephedra" or other botanical ephedrine alkaloid sources, 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 8.1.9 *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 HFP. 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 HFP/ODSP (ODSP@fda.hhs.gov), and industry web-based submission link: https://www.hfpappexternal.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 HFP for evaluation.

2) Products that contain a new dietary ingredient (NDI) without the required NDI notification submission (Section 413 of the FD&C Act), and products that contain ingredients listed on the Dietary Supplement Ingredient Directory.

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 as required.

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 HFP or OII active assignments, or as directed for compliance purposes.

When requesting HFP reviews for compliance cases of bulk ingredients to be used in the manufacturing of a dietary supplement, the labels would need to include the finished product information including serving size, frequency, direction of use, intake, etc… HFP/Office of Surveillance Strategy and Risk Prioritization (OSSRP) requires this information to perform a reliable health hazard assessment and policy determination for contamination exposure.

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 HFP/OCE/OE, 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 Atlanta Human and Animal Food Laboratory (ATLHAFL) 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.**

Microbiological Analysis by USP methods

Collect a sample for microbiological analysis if the product is suspected of having microbial contamination (such as *Salmonella* species*, Escherichia coli, Staphylococcus aureus, Clostridium* species, or yeast and mold). The following methods could be used for the microbiological analysis of the collected samples.

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 Office of Laboratory Operations and Applied Science (OLOAS)/Office of Regulatory Testing and Surveillance (ORTS) 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 HFP to complete a full evaluation of a dietary supplement's label.

When requesting HFP reviews for compliance cases of bulk ingredients to be used in the manufacturing of a dietary supplement, the labels would need to include the finished product information including serving size, frequency, direction of use, intake, etc… HFP/OSSRP requires this information to perform a reliable health hazard assessment and policy determination for contamination exposure.

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/livestock-poultry-disease/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/contact/trade.

Dietary Ingredients of Concern

HFP, in conjunction with OII, 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 the Dietary Supplement Ingredient Directory should be documented by label examination (LEX) and submitted for regulatory consideration in CMS. Divisions should contact Dietary Supplement Enforcement Branch (DSEB) directly for any questions regarding the status of an 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 major food 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 bear disease claims in the labeling of products. Import alert 23-15, "Detention Without Physical Examination of Food Products That Are, or That Contain, Areca (Betel) Nuts, Including Finished Dietary Supplements and Bulk Dietary Ingredients", may be applicable to dietary supplements. 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 4.7 '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 OLOAS/ORTS Program Manager. Samples for Ephedrine Alkaloid Analysis should be directed to Arkansas Human and Animal Food Laboratory (ARHAFL) as the primary servicing laboratory, and Seattle Human and Animal Food Laboratory (SEAHAFL) as the back-up laboratory.

2. Reporting

Establishment inspection reports must be completed in eNSpect per IOM subchapter 5.7.1 '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 and Inspections' 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 ARKHAFL is the primary servicing laboratory and SEAHAFL is the back-up laboratory. Currently, for Microbiological USP analysis the Analytical lab will be directed by OLOAS/ORTS Program Manager.

2. **Analyses to be Conducted**

   Nutrient Analysis/Nutrition Sample Reporting
   (NIS) Dietary Supplements Analysis (Ephedrine Alkaloid) (DIS) Dietary Supplement
   Microbiological Analysis (MIC)

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 (µg/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 ARKHAFL 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 HFP 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, HFP Program Contact and OAMT 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 and regulations (including those relating to new dietary ingredients and other ingredients) and to gain prompt voluntary correction of violations and/or deficiencies. Regulatory recommendations such as Warning Letters or Untitled Letters are taken by HFP using MARC-CMS 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 an OII 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 OII division should immediately contact HFP/OCE and Office of Policy, Compliance, and Enforcement/Division of Compliance and Enforcement (OPCE/DCE) 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 HFP 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 HFP/OCE:

GMP Violations

<u>Manufacturers of dietary supplements:</u>

- 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

HFP/OCE may consider issuing Warning Letters 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.

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

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

HFP/OCE/OE should prepare Warning Letter to firms whose product(s) are intended to supplement the diet but:

- 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 HFP 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 major food allergen as required.
- 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. 3), or
   - The sample does not comply with the requirement in 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 reporting. 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 OHFI CSO should document in the EIR and submit for review according to current procedures. If the firm has performed the requirements but the documentation or actions appear to be inadequate, the OHFI CSO should document in the EIR and consider submitting for review according to current procedures..

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, OII/OHFI should discuss the findings with the HFP/OCE contact. If appropriate, OII/OHFI should request consultation.

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:

HFP/OCE 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 OII 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 HFP 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.

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 HFP. 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 OII 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 OII 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.

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 OII/OHFI division, and HFP/OCE and OII/OHFI 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.

HFP/OCE should submit any recommendation for enforcement follow-up through CMS. If HFP 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 HFP, a meeting will be scheduled between the divisions and HFP/OCE/OE.

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 significant misbranding violations according to RPM Chapter 4 - Advisory Actions. **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 request of HFP/OCE or at the division's discretion.
Prior to initiating the re-inspection, divisions should hold an enforcement strategy discussion with HFP/OE, OII/OHFI 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 enforcement action based on these repeat offenses. Divisions should initiate a call with HFP/OCE/OE, and OII/OHFI 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 OII'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(f)(1)(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 Sections 201(qq) and 403(w) of the Act

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. Guidance on Evidence Development and Documentation to Support Regulatory Action
   D. CGMP Requirements Applicable to Operations Performed by Firm
   E. PAC Usage Decision Tree

3. **Program Contacts**

HFP

Purpose	Name	Organization	Contact
General Program Guidance	Joshua Adams	HFP/OCE/OCOI/CPAB	312-596-4166
Enforcement Guidance	Quyen Tien	HFP/OCE/OE/DCFDSE/DSEB	215-717-3705
Laboratory Technical Information	Guodong Zhang	HFP/OLOAS/OAMT/DFES/MMDB	240-402-2943
Technical Information	Haijing Hu	HFP/OFCSDSI/ODSP	301-796-6555
Laboratory Technical Information	Zachary Miller (Micro) Yanxuan (Tina) Cai (Chemistry)	HFP/OLOAS/ORTS/DSPC/MB HFP/OLOAS/ORTS/DSPC/CB	303-236-9694 240-402-1369
Technical Information	dsTAN	HFP/OFCSDSI/ODSP	See part II(2)(F)

OII

Purpose	Name	Organization	Contact
Domestic/Foreign Guidance National Expert	Siobhan Taylor	OII/OHFI/OGSHFI/HFNES	303-236-3015
Domestic/Foreign Guidance National Expert	Gary Pecic	OII/OHFI/OGSHFI/HFNES	303-236-9601
Domestic/Foreign Guidance Program Expert	Rupa Pradhan	OII/OHFI/OGSHFI/DCFS/HFPEB	781-281-4843
Import Operations and Compliance	FDA Imports Inquiry	OII/OIO/DIO and DAPE	301-796-0356
Technical Information	dsTAN	OII/OHFI	See part II(2)(F)

PART VII - HFP 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 and Enforcement with regard to program priorities, relevant evaluation questions, and recommended program changes. The Office of Compliance and Enforcement 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 and Enforcement will make these evaluations available as well as FSMA Tracker reports that can be run annually or as frequently as needed to track accomplishments.

Working in conjunction with the Program Office, the Compliance Program and Assignments Branch (CPAB) of the Division of Compliance Implementation (DCI) will prepare a yearly summary report for this compliance program. The summary will outline the Program Office's current objectives, highlight their accomplishment data for the year, and list recommendations for the upcoming year. The report will be made available on the Inside.FDA intranet site under the Programs and Initiatives page:
https://fda.sharepoint.com/sites/insideFDA-HFP-Office-of-Compliance-and-Enforcement/SitePages/Compliance%20Programs%20Sub%20Pages/Compliance-Program-Summaries.aspx

Change History

Item	Change	Date
1	Created 21008P PAC for Packaging and Labeling inspections	9/18/2024
2	Remove 21008L PAC for Limited Focus inspections	9/18/2024
3	Updated all PACs to ensure adequate coverage and proper evidence development	9/18/2024
4	Updated POCs and hyperlinks	9/18/2024
5	Create Attachment E - PAC Usage Decision Tree	9/18/2024
6	Updated POCs, organizational structure, and hyperlinks	8/18/2025

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 HFP 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.

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)(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).
- 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.2 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)].

      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 HFP] 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, soybeans, and sesame, 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, soybeans, and sesame, 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.

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 – GUIDANCE ON EVIDENCE DEVELOPMENT AND DOCUMENTATION TO SUPPORT REGULATORY ACTION

- 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/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual (Chapter 2- see 2.5.11 – Detention Powers and Criteria for Detention, 2.10.1 Human Food, 2.10.2 Human Drugs), Chapter 5- See 5.10.7.5 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 D – 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 diseases 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.
   b. Evaluate the reference standards and the characterization process of the reference standards if firm develops in-house reference standards.
   c. Review if laboratory record reflects the analytical results used to support disposition decisions.
   d. 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. Access 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.
      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.