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

SUBJECT:	**IMPLEMENTATION DATE**
DIETARY SUPPLEMENTS—IMPORT AND DOMESTIC	Upon Receipt
	COMPLETION DATE
	Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
INDUSTRY CODE 54		
	21008	for all inspections of dietary supplement firms not subject to Part 111 and all sample collection and analyses
	21008A	for all inspections of dietary supplement firms conducted under Part 111
USE APPROPRIATE PRODUCT CODES	21R829	for all activities involving nutritional health fraud

FIELD REPORTING REQUIREMENTS

For NAI and VAI inspections, within 30 days after completion of each inspection, notify CFSAN via e-mail to ~~Brenda.Aloi@fda.hhs.gov~~ Mallory.Kelly@fda.hhs.gov that the EIR is completed in Turbo EIR. Provide the firm name, FEI and the inspection completion date in the e-mail.

For OAI inspections, prepare and submit a recommendation in the Compliance Management Services (CMS) in accordance with the Regulatory Procedures Manual (RPM) timeframes.

FACTS/OASIS REPORTING

Report all operations both domestic and import under the above PACS.

When reporting import operations, time spent reviewing import labels that does not result in a sample collection must be reported as an import field exam (OASIS #23). Time spent collecting labels, records, or other documentation for submission to the Compliance Branch for review is to be reported as an import sample collection paper (OASIS #41). Do not include time spent reviewing the import label under operation #41. Time spent reviewing the label will be included as OASIS #27 and reported along with the compliance review time as OASIS #43.

PART I - BACKGROUND

General

The term “dietary supplement” is defined in section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act) as a product (other than tobacco), intended to supplement the diet, that bears or contains one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract or combination of any ingredient described above. A dietary supplement is intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form, or if not intended for ingestion in such a form, is not represented for use as a conventional food or as a sole item of a meal or the diet and is labeled as a dietary supplement. A dietary supplement also may *not* contain an article that is an approved drug or that is authorized for investigation as a new drug, and for which substantial clinical investigations have been initiated and have been made public, unless that article was marketed as a food or a dietary supplement prior to its approval as a new drug or authorization as an investigational new drug.

The Dietary Supplement Health and Education Act (DSHEA) of 1994 established a framework for regulating the safety of dietary supplements. Dietary ingredients in or intended for use in, dietary supplements are excluded from the definition of a "food additive." Therefore, deeming a substance that is a dietary ingredient to be an unapproved food additive is not an appropriate reason for recommending enforcement action against a dietary supplement. However, other ingredients in dietary supplements, that are not dietary ingredients within the meaning of section 201(ff)(1) of the Act (e.g., colors, flavors, technical additives, etc.), are still subject to the food and color additive provisions of the Act.

Section 402(f)(1) of the Act places the burden on FDA to prove that a dietary supplement presents a significant or unreasonable risk of illness or injury under the labeled conditions of use or that it contains a substance that may render it injurious to health (under section 402(a)(1) of the Act.

The Food and Drug Administration (FDA) has the authority under section 402(g)(2) of the Act to promulgate current good manufacturing practice (CGMP) regulations for the dietary supplement industry. The Agency proposed Dietary Supplement (DS) CGMP regulations in the March 13, 2003 Federal Register (68 FR 12157). Final CGMPs for dietary supplement were published on June 25, 2007 (72 FR 34751).

Some of the highlights of the final rule are:

- Establishment of minimum requirements for personnel, physical plant and grounds and equipment and utensils;
- Requirements for establishing and following written procedures for certain operations, including those related to equipment, physical plant sanitation, certain manufacturing operations, quality control, laboratory testing, packaging and labeling, and product complaints;
- Requirements for identity testing of dietary ingredients and testing a subset of the finished product batches to determine that they meet product specifications;
- Establishment of specifications in the production and process control system;
- Requirements for implementation of quality control operations; and
- Requirements for the preparation and use of written master manufacturing records and batch production records.

Compliance with the new DS CGMP's is based on the number of employees of a firm as follows: June 25, 2008 for firms employing 500 or more employees; June 25, 2009 for firms employing fewer than 500 but more than 20; and June 25, 2010 for firms employing fewer than 20 employees.

Adverse Event Reporting

On December 22, 2006, the President signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Pub. L. 109-462).

The law has four major provisions (1) requires the collection of all adverse event reports by manufacturers, distributors, and retailers of dietary supplements; (2) requires the reporting of serious adverse event reports to the FDA; (3) requires firms to maintain records of reports of all adverse events and requires that FDA be allowed to inspect those records; and (4) requires that dietary supplement labels bear information to facilitate the reporting of serious adverse events associated with the use of dietary supplements by consumers.

The requirements of this law became effective on December 22, 2007, one (1) year after the date of enactment of the law.

Investigators are asked to make the firm aware of the passage of this law and direct them to the two guidance documents published in June 2009 and September 2009.

Edible Ruminant Products from BSE Affected or At Risk Countries

FDA regulations prohibit the use of certain cattle materials in foods, including dietary supplements (see 21 CFR 189.5). Prohibited materials include specified risk materials (e.g., brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, of the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum), the dorsal root ganglia of cattle 30 months and older and the tonsils and distal ileum of the small intestine of all cattle, mechanically separated beef, small intestine of all cattle (except as provided in 189.5(b)(2), material from non-ambulatory disabled cattle, and material from cattle not inspected and passed.

In addition, final regulations on records for prohibited cattle material were published in the October 11, 2006 Federal Register (71 FR 59653). The new regulation (21 CFR 189.5(c)), among other things, requires firms to maintain records that demonstrate that products are not made with prohibited materials. Records must be maintained for 2 years, and FDA must be allowed to inspect and copy them. These requirements became effective on January 9, 2007.

On February 9, 2001, The United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) further prohibited the importation into the United States of certain edible ruminant products from BSE affected or at risk countries. In support of this ban, FDA issued Import Bulletin (IB) #99-B14 to require that FDA entry review be done to determine whether products offered for entry contain ingredients subject to APHIS prohibition. The Agency believes that steps should be taken by manufacturers to reduce the potential risk of human exposure to, or transmission of, the agent that causes BSE.

Regardless of country of origin, firms should be able to document that non-prohibited bovine-derived ingredients come from animals that have been inspected and passed for human consumption by the appropriate regulatory authority and that at the time it was inspected and passed, it was found to be not adulterated. The failure to have such documentation may cause the material to be a prohibited cattle material under 21 CFR 189.5(a)(2).

If a firm uses bovine-derived ingredients, or uses bovine tissues originating in countries where BSE is known to exist, investigators should examine the firm's records to determine if they have records that document that the substance or ingredient is not a prohibited cattle ingredient or derived from a prohibited cattle material.

New Dietary Ingredient Under DSHEA

Section 413(c) of the Act defines a new dietary ingredient as a dietary ingredient that was not marketed in the United States before October 15, 1994. Section 413(a) states that a dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:

- The dietary supplement contains only dietary ingredients which 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

- 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 the Secretary [and by delegation, 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.

When a notification is required, it must be sent to FDA at least 75 days prior to marketing the product in accordance with the requirements in 21 CFR 190.6. Failing to submit a new dietary ingredient notification to FDA, when required, may cause the dietary supplement containing the new dietary ingredient to be adulterated within the meaning of section 402(f)of the Act.

Dietary Supplements Containing Ephedrine Alkaloids

On February 11, 2004, FDA published a final rule declaring dietary supplements that contain ephedrine alkaloids are adulterated on the basis that these products present an unreasonable risk of illness or injury. The final rule went into effect on April 12, 2005. See 21 CFR 119.1.

Some dietary supplements are labeled to contain "ephedra"; however, the product may not contain ephedrine alkaloids if the plant material is an ephedra that doesn't normally contain ephedrine alkaloids (for example, North American species of ephedra, including Ephedra nevadadensis, contain little or no ephedrine or other alkaloids) or if the ephedrine alkaloids have been

chemically removed. If a product is encountered that states it contains "ephedra," investigators should ascertain from the firm the type of evidence they have to establish that it does not contain any ephedrine alkaloids. If a firm does not appear to have a basis to conclude the product does not contain ephedrine alkaloids (for example, analytical results, certificates of analysis, etc.) a sample should be collected for analysis.

Labeling

A dietary supplement labeling guide is available for viewing on FDA's intranet.

1) All dietary supplement products (with the exception of exempt products) labeled after March 23, 1999, are subject to the labeling requirements of Title 21 Code of Federal Regulations Section 101.36 (21 CFR 101.36). Exemptions from the requirement for nutrition labeling include dietary supplement products manufactured by firms that meet the small business exemptions (21 CFR 101.36 (h)(1)(2), e.g., low volume products, and products shipped in bulk (21 CFR 101.36(h)(3)(see ATTACHMENT A)).

2) Firms that believe they are entitled to an exemption from nutritional labeling for low-volume dietary supplement products for small businesses must file a notice claiming the exemption and provide the information necessary to verify their exempt status to the Center for Food Safety and Applied Nutrition/Office of Nutrition, Labeling and Dietary Supplements (CFSAN/ONLDS), unless they are automatically exempt. The home district for the firm receives a copy of the firm's notice and ONLDS' acknowledgement.

3) A dietary supplement must be identity labeled using the term "dietary supplement" or an alternative form permitted by regulation (see 21 CFR 101.3(g)). For example, an appropriately descriptive term indicating the type of dietary ingredients in the product could be used to replace the word "dietary" (such as herbal supplement, or herbal supplement with vitamins, etc.).

4) Dietary supplements that contain botanical ingredients must also comply with specific nomenclature rules for the botanical ingredients that specify how the botanical ingredients must be identified and that require that the part of the plant used (e.g., root, leaves, etc.) be disclosed (See 21 CFR 101.4(h)).

5) Dietary supplement products in solid oral dosage form, e.g., tablets or capsules, that contain added iron or iron salts for use as an iron source must bear a label warning statement (21 CFR 101.17(e)(1)). In 1997, FDA finalized a rule that required unit-dose packaging of dietary supplements containing added iron and iron salts (see 21 CFR 111.50 (a)). On January 21, 2003 the US Court of Appeals for the 2nd Circuit issued a decision that FDA lacked authority to issue the regulation and remanded the case to the District Court to fashion an appropriate remedy. On May 9, 2003, the Court entered an order declaring the regulation invalid. FDA withdrew the unit-dose packaging regulation in the October 17, 2003 Federal Register(68 FR 59714).

6) The Farm Security and Rural Investment Act of 2002 (Pub. L. 107-171) (Farm Bill) added section 403(u) to the Act. This new paragraph states that a dietary supplement is misbranded if it purports to be or is represented as ginseng, unless it is an herb or herbal ingredient derived from a plant classified within the genus Panax. Therefore, 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. This means some ingredients that are not Panax spp., but which have included the word "ginseng" as part of their common or usual name may no longer do so. For example, the plant Eleutherococcus senticosus has also

been called Siberian Ginseng. Under new section 403(u) of the Act, this botanical could not use the term "ginseng" in its common or usual name but instead would need to be named in accordance with the requirements of 21 CFR 101.4(h).

7) Dietary supplements also need to meet the allergen labeling requirements in the Food Allergen Labeling and Consumer Protection Act of 2004 (Pub. L. 108-282) which require the disclosure of major food allergens. For dietary supplements, major food allergens, if present, may be disclosed in the "other ingredient" list or within the supplement facts panel, if a dietary ingredient.

8) In the December 13, 2006 Federal Register (71 FR 74785) FDA published a final rule that permits "per unit" and "per day" labeling in the supplement facts panel in addition to the usual "per serving" information. A firm must include the "per serving" information in the supplement facts panel, but may optionally also include "per unit" or "per day" information if they choose.

9) Under section 403(r)(6) of the Act, a dietary supplement may bear certain claims, generally called structure/function claims, on its label or in its labeling provided that the firm has substantiation that: the claim is truthful and not misleading; the firm has notified FDA within 30 days of marketing the product bearing the claim; and the claim includes a mandatory disclaimer. At the present time, we are not asking that label claims be examined to determine if they contain the disclaimer because there are unresolved policy issues regarding the use of the disclaimer and, therefore, it is premature to examine whether the required disclaimer is properly used in accordance with 21 CFR 101.93.

10) The Agency will, on a case-by-case basis, consider enforcement actions against products that bear egregious disease claims or structure/function claims that may be unsubstantiated. Investigators should review claims made for dietary supplements on labels or in labeling. Products that bear inappropriate disease claims or that appear to bear egregiously false or misleading structure/function claims should be referred to CFSAN for evaluation.

11) On June 1, 2005, an intercenter agreement was implemented between CFSAN and the Center for Drug Evaluation and Research (CDER) that outlines a working agreement between the two Centers that assigns lead Center status for the regulation of certain products that bear structure/function or disease claims.

12) The preamble to the final rule that published on January 6, 2000 (65 FR 1000)—Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, provides important background and rationale for the Agency's policies related to structure/function and disease claims issues. Districts may want to refer to FDA's website for industry guidance on structure/function claims prepared in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act. This guidance restates in plain language the legal requirements set forth in the January 6, 2000 regulation concerning labeling claims for dietary supplements.

13) Final industry guidance on substantiating claims made for dietary supplements under 403(r)(6) is available on FDA's website.

Imports

Numerous import alerts and bulletins pertaining to dietary supplement ingredients have been withdrawn since the inception of DSHEA. Districts must refer to the FDA website for an up-to-date index of applicable import alerts and bulletins. Available online at: ***http://alpha.ora.fda.gov/fiars/fiars.html (intranet)***
http://www.fda.gov/ForIndustry/ImportProgram/ImportAlerts/default.htm (internet)

Districts should contact the Division of Import Operations and Policy (DIOP), HFC-170, to determine the current status of an applicable import alert or bulletin.

PART II - IMPLEMENTATION

OBJECTIVE

The objectives of the program are as follows:

- To conduct inspections at domestic and foreign dietary supplement firms, using appropriate Current Good Manufacturing Practice regulations.
- To collect and analyze domestic, domestic-import, and import samples of dietary supplements of vitamins, minerals, and proteins to compare label declarations to the nutritional composition of the product.
- To collect information to determine the extent to which dietary supplements are being labeled in accordance with the nutrition labeling ("Supplement Facts" panel) and other labeling requirements.

INTERACTION WITH OTHER PROGRAMS

Include coverage of this program during inspections conducted under CDER's Drug Process Inspection Compliance Program when it is determined that the firm manufactures both drugs and dietary supplements. Use the appropriate CDER and CFSAN Program Assignment Codes (PACS) when reporting time for these inspections, e.g., PAC 56002 for time spent inspecting drug processes and PAC 21008 for time spent inspecting dietary supplement processes.

PROGRAM MANAGEMENT INSTRUCTIONS

To use the planned resources effectively, CFSAN has established priorities for selecting firms to be inspected and dietary supplements to be collected for analysis.

A. Planning Instructions

As an aid to the districts in selecting firms to be inspected, CFSAN's Division of Field Programs and Guidance (DFPG) can provide each district with a print-out listing the known dietary supplement firms in each district. Contact ~~Brenda K. Aloi~~ Mallory Kelly, CFSAN/DFPG at ~~(301) 436-2065~~ (240) 402-2401 ~~brenda.aloi@fda.hhs.gov~~ mallory.kelly@fda.hhs.gov if you would like the print-out for your district.

Firms should be given priority for inspection as follows:

- Firms that blend and fabricate finished dietary supplement products;
- Firms that package and label finished dietary supplement from bulk products;
- Firms that apply the final product label to finished dietary supplement products;
- Firms that perform other operations not listed above on finished dietary supplement products.

B. Select firms for inspection in the following order of priority:

1. Firms producing both dietary supplements such as botanicals (e.g.,ginseng, yohimbe), animal and plant extracts (e.g., garlic extracts and glandulars), fats and lipid substances (e.g., oil of evening primrose, fish oils, essential fatty acids) and also producing dietary supplements such as vitamins, minerals, and proteins;

2. Firms producing dietary supplements such as botanicals (e.g., ginseng, yohimbe), animal and plant extracts (e.g., garlic extracts and glandulars), fats and lipid substances (e.g., oil of evening primrose, fish oils, essential fatty acids) **but not producing** any dietary supplements of vitamins, minerals, or proteins;

3. Firms producing only dietary supplements of vitamins, minerals, or proteins.

The above prioritization scheme, because of its focus on firms manufacturing "non-traditional" products, may not result in sufficient products that meet the threshold for sample collection and analyses under the program, i.e., products which contain 25% of the Reference Daily Intake (RDI) or Daily Reference Value (DRV) of a vitamin, mineral, or protein. ***It is important that districts meet their workplan obligation for sample collections by collecting appropriate samples from other establishment types visited for purposes of conducting field exams (see C below).***

C. Label Exams for Import Products

Districts should refer to FDA's internet site for a list of small business nutrition labeling exemptions before conducting label examinations. All products manufactured by those firms meeting the requirements for an exemption are exempt from nutrition labeling required by 21 CFR 101.36.

Products subject to detention without physical examination due to "Supplement Facts" panel labeling violations will be listed in Import Alert 99-20, "Detention Without Physical Examination of Imported Foods Due to NLEA Violations," which is accessible on the FDA Internet and Intranet.

D. New Dietary Ingredients Under DSHEA

Section 413(c) of the Act defines a new dietary ingredient as a dietary ingredient that was not marketed in the United States before October 15, 1994. Section 413(a) states that a dietary supplement which contains a new dietary ingredient shall be deemed adulterated under section 402(f) unless it meets one of the following requirements:

- The dietary supplement contains only dietary ingredients which 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

- 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 the Secretary [and by delegation, 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.

  When a notification is required, it must be sent to FDA at least 75 days prior to marketing the product in accordance with the requirements in 21 CFR 190.6. Failing to submit a new dietary ingredient notification to FDA, when required, may cause the dietary supplement containing the new dietary ingredient to be adulterated within the meaning of section 402(f) of the Act. General industry directions for filing new dietary ingredient notifications can be found on FDA's internet website.

  The Agency is aware that some dietary supplements may contain new dietary ingredients for which FDA should have received a premarket notification. However, at the present time, the Agency intends to only consider and pursue enforcement actions against such products on a case-by-case basis. CFSAN will identify and develop targeted assignments to address this issue in collaboration with ORA.

PART III - INSPECTIONAL

Refer to Part I. BACKGROUND for more information on the various requirements and areas that must be covered during each inspection conducted under this compliance program. Specific instructions to investigators on each of these areas are provided below.

A. **Inspection**

Compliance with Current Good Manufacturing Practices

Investigators performing inspections under this compliance program must be familiar with the requirements of 21 CFR Part 111 and should have successfully completed the ORA/DHRD training course entitled Dietary Supplement GMP—FDA340. The final regulations on Dietary Supplement GMPs as well as additional background are available on FDA's internet website.

With the exception of very small firms (employing fewer than 20 employees), effective June 25, 2009, all firms engaged in the manufacturing, packaging, holding and distributing of **finished dietary supplements** will be subject to the GMP regulations contained in Part 111. After June 25, 2010, firms with fewer than 20 FTE employees must be in compliance with Part 111.

> Note: Firms manufacturing, packaging, holding, or distributing dietary supplement ingredients, but **no** finished dietary supplements are to continue to be inspected under the General Food GMP Requirements of Part 110.

Evaluate the firm's compliance with GMP requirements. Cover all items that are applicable to the types of operations being performed in the firm being inspected. Firms must comply with the subparts of the DS GMPs that apply to its operations related to the manufacture, packaging, labeling, and holding of dietary supplements. Not all requirements will be applicable in each firm. The operations being conducted in the firm will determine which specific subparts of the regulations apply.

Investigators must use their experience and expertise to guide the inspection and to make decisions on how the inspection should be focused.

The Establishment Inspection Report (EIR) should include a sub-heading for each of the underlined categories covered and sufficient details regarding each of the numbered items should be included under the sub-heading to verify that the categories were adequately addressed during the inspection.

Initial Interview

1) Determine number of full-time equivalent employees.

- Count employees located at the facility being inspected as well as all employees at other corporate facilities owned by the same corporate entity;
- If the business operating the facility being inspected is an independently operated subsidiary of a larger holding company or corporate entity, count only employees of the subsidiary (all locations of the subsidiary);

- Do not count employees of firms ***contracted*** to perform any operations of the firm being inspected.

Questions on determining the number of full-time equivalent employees should be directed to Brad Williams, CFSAN/ONLDS, ~~301-436-1440~~ (240) 402-1440 or Brad.Williams@fda.hhs.gov.

2) Determine the types of operations performed on finished dietary supplements.

3) Determine the types of products the firm handles and select a minimum of 2 products to inspect and review manufacturing records, including at least one product containing a botanical ingredient. The botanical ingredients listed on Attachment E of this assignment should be given higher priority for coverage

Note: This inspectional directive is not all inclusive, but highlights new requirements of the DS GMP (e.g. written procedures, QC requirements, etc). You should evaluate the firm's compliance with all GMP requirements.

The firm's quality control operation has responsibilities in all subparts of this regulation. Report on QC operations in Subpart F - Quality Control section below.

Personnel, Physical Plant and Equipment and Utensils

Subpart B - Personnel

4) Does the firm have written procedures for preventing microbial contamination, and hygienic practices for employees and are they followed? (Section 111.8)

5) Review training documentation of employee(s) that includes date of training and type of training. (Section 111.14).

6) Determine who is responsible for quality control operations and their qualifications. (Section 111.12(b))

Subpart C – Physical Plant and Grounds

7) Review written procedures for cleaning the physical plant and pest control. (Section 111.16)

8) If water is a component of the dietary supplement, review water records to make sure that the water complies with applicable Federal, State, and local requirements. (Section 111.15e)

9) Determine if there is an assigned qualified sanitation supervisor. (Section 111.15k)

Subpart D – Equipment and Utensils

10) Has the firm determined if automated, mechanical or electronic equipment used in manufacturing, packaging etc., is capable of operating

satisfactorily within the operating limits required by the process? (Section 111.30b)

11) Are appropriate controls established for this equipment (including software on a computer controlled process) to ensure that changes are approved by QC personnel and instituted only be authorized personnel? (Section 111.30d)

12) Are there established and appropriate controls to ensure the equipment functions in accordance with its intended use? (Section 111.30e)

13) Does the firm have written procedures for calibrating instruments, controls and equipment used for measuring components, and for the manufacturing of a dietary supplement, and are they followed? (Section 111.25a, b)

14) Does the firm have written procedures for cleaning, sanitizing (if necessary), and maintenance of all equipment and utensils and contact surfaces, and are they followed? (Section 111.25c) Review equipment logs or batch records for documentation of data of use, maintenance, cleaning and sanitation of equipment. (Section 111.35(b)(2)

15) If the firm uses freezers, refrigerators, or other cold storage compartments to store components or finished batches of dietary supplements do they have a thermometer or temperature-recording device to allow for recording of the temperature, and is there an automated device for regulating temperature or an automated alarm on a manual system? (Section 111.27a)

16) If the firm uses wet processing do they clean and sanitize all contact surfaces, before use, and after any interruption during which the contact surface may have become contaminated (Section 111.27d)

Production and Process Controls Systems

Subpart E – Requirements to Establish a Production and Process Control System

The production and process control system must include the requirements of subparts E through L of Part 111, and must be reviewed and approved by QC personnel.

17) Determine what specifications the firm has established for components, in process materials, labels, packaging components, and finished products being inspected. (Section 111.70)

18) Are they conducting at least 1 appropriate test or exam on each dietary ingredient to verify its identity and review the results of the tests or exam for the dietary ingredients? (Section 111.75(a)(1)

19) Review the results of the firm's qualification of the supplier of the components, and review Certificates of Analysis for the incoming materials. (Section 111.75a)

20) Review the firm's in-process specifications and finished product specifications, and determine if the specifications demonstrate that the product has the appropriate identity, purity, strength, and composition. (Section 111.75)

21)Review firm's documentation of the result of appropriate tests or exams to ensure that the finished batch product specifications (either subset of batches or all batches) are met in the manufacturing of the product. (Section 111.75b and c)

22)If the firm exempts one or more product specifications from the verification requirements did they document why any component and in-process testing, exam, or monitoring will ensure that the product meets its specifications. (Section 111.75d)

23)Does the firm collect representative and reserve samples as required? (Sections 111.80 and 111.83)

Subpart F – Quality Control

Has the firm established written procedures for the quality control operations? (Section 111.103)

Production and Process System

24)Determine if QC personnel reviewed and approved the documentation setting forth the basis for the following:
   a. supplier qualification. (Section 111.105b)
   b. why meeting in-process specifications will help ensure that the identity, purity, strength, and composition of the dietary supplement are met. (Section 111.105c)
   c. why the results of appropriate tests or examination for each product specifications selected will ensure that the finished batch of dietary supplement meets product specifications. (Section 111.105d)
   d. why any product specification is exempted from the verification requirement, and why any component and in-process testing, examination, or monitoring, or other methods will ensure that such exempted product specification is met without verification through periodic testing of the finished batch. (Section 111.105e)

25)Do QC personnel determine whether all manufacturing specifications (e.g., to control any points, steps, or stage) are met? (Section 111.105h)

Laboratory Operations

26)Determine if QC personnel reviewed and approved all laboratory control processes associated with the production and process control system. (Section 111.110a)

27)Do QC personnel ensure that all tests and examinations are conducted for established specifications and approve all results of these tests and examination? (Section 111.110b and c)

Material Review and Disposition

28)Review the documentation of any material reviews and disposition determinations. Determine the corrective actions taken and disposition of the material. (Section 111.113)

Equipment, Instruments and controls

29)Do QC personnel review and approve all processes for calibrating instruments and controls; and periodically review calibration records, and inspection/checks of automated, mechanical or electronic equipment? (Section 111.117)

Components, Packaging and Labeling

30)Do QC personnel determine whether all components, packaging, and labels conform to established specifications, and make required disposition decisions? (Section 111.120)

31)Do QC personnel approve or reject any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement, and the disposition of any rejected materials? (Section 111.120d)

32)Do QC personnel approve and release from quarantine, all components, packaging, and labels before they are used? (Section 111.120e)

Master Manufacturing Record, Batch Record and Manufacturing Operations

33)Do QC personnel review and approve all master manufacturing records and all modifications to the master manufacturing records? (Section 111.123(a)(1))

34)Do QC personnel review and approve all batch production-related records? (Section 111.123(a)(2))

35)Do QC personnel review all monitoring for the production and process control system? (Section 111.123(a)(3))

36)Do QC personnel determine whether all in-process specifications established are met? (Section 111.123(a)(6))

37)Do QC personnel determine whether each finished batch conforms to established product specifications (Section 111.123(a)(7)) and approve and release, or reject, each finished batch for distribution, including any reprocessed finished batch? (Section 111.123(a)(8)

Packaging and Labeling

38)For re-packers who distribute the product (rather than return it to supplier), do QC personnel review receipt documentation, and the results of a visual examination to ensure that established specifications are met; and approve and release the product from quarantine before they are used for packaging and labeling? (Section 111.127(a) &(b)?

39)Do QC personnel review and approve all records for packaging and labeling operations? (Section 111.127(c)

40)Do QC personnel determine whether finished packaged and labeled dietary supplement conform to established specifications, and approve for release (or reject)? (Section 111.127(d)

41)Determine if quality control operations conducted a required material review and made a required disposition decision for repackaging of a packaged dietary supplement, or re-labeling of a packaged and labeled dietary supplement. Determine if quality control operations approved for

release or rejected any packaged and labeled dietary supplement for distribution (Section 111.127).

Returned Dietary Supplements

42)40) Do QC personnel conduct a required material review and make a required disposition decision for returned dietary supplements? (Section 111.130(a))

43)Do QC personnel approve or reject

a. salvage and redistribution of returned dietary supplement? (Section 111.130(b)
b. reprocessing of returned dietary supplement? (Section 111.130(c)

44)Do QC personnel determine whether reprocessed dietary supplements meet product specifications and either approve for release, or rejected, any returned dietary supplement that was reprocessed? (Section 111.130(d)

Product Complaints

45)Do QC personnel review and approve decisions about whether to investigate a product compliant and review and approve the findings and follow up action of any investigation performed? (Section 111.135)

Subpart G – Components, Packaging and Labeling

46)Does the firm comply with the requirements for incoming components of dietary supplements (Section 111.155) and with requirements for packaging and labels received (Section 111.160); including examination, quarantine, collection of representative samples, QC review and approval, and use of identifiers to allow for trace back of each unique lot to the suppler?.

47)For re-packers: Does the firm comply with requirements for product(s) received for packaging or labeling [Section 111.165, and rejected components packaging and labeling? (Section 111.170)

48)Does the firm make and keep records required under this subpart, including, written procedures, receiving records, and documentation that requirements of this subpart were met (Section 111.180)

Subpart H – Master Manufacturing Record

A Master Manufacturing Record (MMR) is required for each unique formulation of DS manufactured, and for each batch size.

For the product(s) inspected:

49)Review the master manufacturing record (MMR) and determine if the firm has included the following:

a. Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure quality of the product and that the supplement is packaged and labeled as specified in the MMR (Section 111.210)
b. Controls and procedures to ensure that each batch of dietary supplement meets the established specifications. (Section 111.205)

50)Does the MMR include all of the required information? (Section 111.210)

Subpart I – Batch Production Record

51)Has the firm complied with the requirements for the batch production records? (Section 111.255)

52)Review a representative number of batch records from the date of implementation of the regulation to determine if batch records are complete (Section 111.260).

Subpart J – Laboratory Operations

53)Does the firm have written procedures for laboratory operations, including procedures for the tests and examination to determine if specifications are met? (Section 111.303)

54)Are laboratory control procedures established and followed in accordance with Section 111.315, e.g. criteria for establishing appropriate specifications, use of sampling plans, etc.

55)Are scientifically valid laboratory methods used for testing and examination? (111.320)

56)Does the firm conduct and document tests or examinations to ensure that specifications are met? (Section 111.325)

Subpart K – Manufacturing Operations

57)Has the firm established and do they follow written procedures for manufacturing operations? (Section 111.353)

58)Does the firm take appropriate precautions to prevent against contamination of components or dietary supplements? (Section 111.365)

59)Does the firm clearly identify, hold, and control under a quarantine system all incoming components, products awaiting disposition decisions by quality control personnel and any rejected dietary supplements? (Section 111.370)

Subpart L – Packaging and Labeling Operations

60)Does the firm have and do they follows written procedures for packaging and labeling operation? (Sections 111.403 and 111.430). These procedures should include the following:
   a. Control, issuance, and reconciliation of labels (Section 111.410)
   b. Examination of packaging and labels to ensure they meet the specifications in the MMR (Section 111.410)
   c. Ensuring that products are not contaminated during the packaging and labeling operations (Section 111.415)
   d. Assigning a batch, lot or control number to each lot of dietary supplement (section 111.415)
   e. Ensuring that the firm can determine the complete manufacturing history and control of the dietary supplement through distribution (Section 111.410(d))

Subpart M—Holding and Distributing

61)Has the firm established and do they follow written procedures for holding and distributing operations? (Section 111.453)
62)Does the firm hold product under appropriate conditions so the identity, purity, strength and composition of the dietary supplement are not affected? (Section 111.455)

63)Does the firm maintain distribution records, as required? (Section 111.475)

64)Review the firm's reserve samples to ensure they are appropriately held to protect from contamination and deterioration (Section 111.465(a) and that they are held in the same container closure system in which the packaged and labeled dietary supplement is distributed (Section 111.465(a)(2).

Product Complaints and Returns

Subpart N – Returned Dietary Supplements (See AER Below)

65)Has the firm established and do they follow written procedures for returned dietary supplements? (Section 111.503)

66)Does the firm perform and document material reviews and disposition decisions on returned dietary supplements? (Section 111.535b)

67)For reprocessed dietary supplements, does the firm perform and document testing or examination conducted to determine compliance with product specifications and reevaluation by QC personnel? (Section 111.535)

Subpart O – Product Complaints (See Adverse Event Reporting Below)

68)Does the firm have, and do they follow written procedures for product complaints? (Section 111.553)

69)Does the firm investigate any product complaint that involves a possible failure of a dietary supplement to meet product specifications, and does the investigation extend to all relevant batches and records? (Section 111.560)

70)Review records of product complaints related to CGMPs and corrective actions taken.

Adverse Event Reporting

On December 22, 2006, the President signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Pub. L. 109-462). The reporting requirement is Section 761 of the FD&C Act.

The requirements of this law became effective on December 22, 2007, one (1) year after the date of enactment of the law.

Investigators are asked to make the firm aware of the passage of this law and direct them to the two guidance documents published in June 2009 and September 2009. The guidance documents may be viewed on FDA's internet website.

Investigators are requested to cover the following points during each inspection and to include details of such coverage in the inspection report:

- Assure that the firm is aware of the passage of this law. Provide link to above industry guidance document;

- 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; Districts should follow procedures noted in Part V.

- Determine if the firm has a prominent statement informing consumers that they may report serious adverse events to the domestic address or domestic phone number on the label. While there is no specific requirement for this statement, FDA has recommended in the guidance on this subject that firms include such a statement on the label. In addition, firms may provide an email address or website on the product label to which reports may be made, provided that such email address or website is in addition to the domestic phone number or domestic address that is required by statute. If the firm does not have the recommended prominent statement, they should be made aware of the recommendation and the ways described above that it can be accomplished.

- Determine if the firm has a record keeping system in place for maintaining records of adverse event reports. The above guidance documents contain specific requirements for what records must be maintained and the retention period.

- Determine if the firm has a process in place to report serious adverse events.

- Determine whether the firm has submitted any reports to FDA since the rule became effective, or since the date of the previous inspection within established timeframes.

- Determine whether the firm has any adverse event reports that appear to be serious and for which they have not submitted a report to FDA.

Edible Ruminant Products from BSE Affected or At Risk Countries

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

If an investigator encounters any one of the conditions below related to use of a bovine-derived ingredient, the following evidence must be collected and forwarded to CFSAN for further regulatory consideration.

1) A bovine-derived ingredient is a prohibited cattle material under 21 CFR 189.5(a) if it is a specified risk material that has not been inspected

and passed for human consumption by a competent authority or is otherwise a prohibited material under 21 CFR 189.5(a). Affirmative evidence of the use of prohibited cattle material must be collected.

2) If the firm is using bovine-derived ingredients, they must have records to show that the food is not manufactured from, processed with, or does not otherwise contain prohibited cattle materials (21 CFR 189.5(c)). Documentation of the lack of these records must be collected.

3) Under the new dietary supplement CGMP regulations, firms must establish specifications for animal-derived ingredients that are necessary to ensure the quality of the dietary supplement. Firms must also take necessary actions to determine that specifications are met. If such specifications are not established or met, collect adequate documentation of the deficiency.

Dietary Supplements Containing Ephedrine Alkaloids

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

2) If a product claims to contain ephedrine alkaloids or contains "ephedra" and the firm does not appear to have evidence that it does not contain ephedrine alkaloids, the inspection should specifically cover the following items:

- Collection of interstate documentation of the products shipped from the manufacturer or supplier to the firm (this information should be tied into an affidavit).
- From whom does the firm obtain products?
- Where does the firm warehouse their products?
- What volume of product do they buy and sell?
- Do they sell to consumers only or also to other distributors?
- Is the product being offered for sale through sponsored websites?
- Collect all labeling, ads, and promotional material currently used.

3) If the firm does not manufacture the products, the district should attempt to get information from the firm about their supplier. If the suppliers are not located in the same district, the district should issue an assignment to the home district 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 Sample Collections

B. Import and Domestic Field Exams

Products shipped in bulk form, not distributed to consumers in such form, and used in the manufacture of other dietary supplements are exempt from the requirements for nutrition labeling ("Supplement Facts" panel)(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.

Firms that have filed a small business exemption notice with CFSAN will be issued an acknowledgement letter. A copy of each acknowledgement letter will be sent to the home district for the firm. Investigators must review the firm jacket prior to conducting inspections to determine whether the firm has been issued an acknowledgement letter from CFSAN. Investigators must verify the firm's status with firm management after issuing the FDA 482, but prior to conducting any field exams. Do not conduct field exams in firms that are exempt from compliance.

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

Investigators conducting field exams must refer to the list of firms that have filed for an exemption from nutrition labeling requirements before conducting label examinations.

Specific questions about the exempt status of a domestic firm, importer, or broker should be directed to CFSAN/ONLDS/Division of Food Labeling and Standards (DFLS) (HFS-820), ~~(301) 436-1690~~ (240) 402-1690.

Review the label of 2-3 non-exempt 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 that fail to bear nutrition labeling, 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).

2) Products that fail 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 (21 CFR 101.3(g)).

3) Products that 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.

   The Agency will, on a case-by-case basis, consider enforcement actions against products that bear egregious disease claims or structure/function claims that may be unsubstantiated.

   Investigators should review claims made for dietary supplements on labels or in labeling. Products that bear inappropriate disease claims or that appear to bear egregiously false or misleading structure/function claims should be referred to CFSAN for evaluation.

4) Products that bear authorized health claims or nutrient content claims that do not qualify for making the claims.

5) Products that bear nutrition ("Supplement Facts" panel) labeling with significant format deviations (21 CFR 101.36).

6) Products in solid dosage form with added iron or iron salts that fail to bear the required warning statement (21 CFR 101.17(e)(1)).

7) Products that use the term “ginseng” but are ineligible to do so.

8) Products that fail to disclose a required major food allergen.

9) Products that fail to bear other mandatory label information.

10) Failure to maintain adequate records by firms that manufacture dietary supplement containing cattle derived material.

11) Products that appear to contain a source of ephedrine alkaloids.

C. Import Investigations

Domestic Contact for Adverse Event Reporting

On December 22, 2006, the President signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Pub. L. 109-462). The requirements of this law became effective December 22, 2007. One of the four major provisions of this law requires that dietary supplement labels bear information to facilitate the reporting of serious adverse events associated with the use of dietary supplements by consumers. Under this new law, the label for any dietary supplement that is marketed in the United States must include a domestic address or domestic phone number through which the responsible person may receive a report of a serious adverse event with such dietary supplement. During label exams of imported dietary supplements, determine whether the label includes the appropriate contact information.

Edible Ruminant Products from BSE Affected or At Risk Countries

Refer to the guidance contained in IB #99-B14. Be alert for shipments subject to the APHIS prohibitions covered by this import bulletin. Refer such entries to USDA/APHIS Plant Protection Quarantine (PPQ) Headquarters via the fax back form to 301-734-8538.

Investigators must also be alert for entries that are not being appropriately declared as BSE ruminate product on entry. If product is not being accurately declared on entry, DIOP should be advised for appropriate action.

New Dietary Ingredients Under DSHEA

The Agency will identify candidate ingredients through import alerts, directed assignments, or guidance. Entries of new dietary ingredients or dietary supplements containing new dietary should be recommended for detention by the district.

Dual Language Labels

Attention should be given to imported product labels for accuracy in translation of ingredients from the foreign language to English to determine if the translation correctly describes all ingredients, particularly with regard to declaration of allergens, BSE and herbal/botanical ingredients, FD&C Yellow Nos. 5 and 6 and sulfites. If the district does not have a staff member who can translate, please notify the General Program contact person for assistance.

Ingredients Subject to Import Alerts

Numerous import alerts are in effect for dietary supplement ingredients, including but not limited to IA 54-13 “Detention without Physical Examination of Dietary Supplements and Bulk Dietary Ingredients Containing Ephedrine Alkaloids”; IA 54-11 “Detention without Physical Examination of Bulk Dietary Ingredients and Dietary Supplements Containing Androstenedione”, and IA 54-10 “Detention without Physical Examination of Bulk or Finished Dietary Supplements and other Products that may Contain Aristolochic Acid. In addition, some import alerts coded under industries 60-66 (CDER codes) may be applicable to dietary supplements as well.

Import investigators must refer to the FDA website to obtain a complete listing of Import Alerts and Bulletins applicable to dietary supplements and their dietary ingredients. ***Available online at:***
http://alpha.ora.fda.gov/fiars/fiars.html (intranet)

http://www.fda.gov/ForIndustry/ImportProgram/ImportAlerts/default.htm (internet)

D. **Sample Collection**

Documentary samples (paper samples in OASIS) collected under Area of Emphasis Nos. 1, 2, 3, 5, 6, 7, 8 and 9 will generally consist of the label only; no physical sample is required.

NOTE: 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. Collect one (1) product container along with the four (4) original product labels.

1) Compliance Samples

a) Areas of Emphasis Nos. 1, 2, 3, 5, 6, 7, 8 and 9

i. Collect a sample of any product that appears, on the basis of the field exam (see **B. Import and Domestic Field Exams**) to be deficient under one or more of the above Areas of Emphasis.

ii. Import lots sampled for a deficiency under one of the above areas shall not be released; rather they shall remain subject to the terms and conditions of the importer's entry bond pending compliance review.

iii. The sample will consist of four (4) original labels (and one product container, if warranted) for the product being sampled. 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.

iv. For samples collected for undeclared allergens (Area of Emphasis 8) 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, and final product label.

v. Indicate "Compliance" in the **Basis** field of the C/R. Under **Reason for Collection** indicate "Label Review Only."

vi. Send the sample to your compliance branch for label review, sample classification, and regulatory consideration.

b) Area of Emphasis No. 4

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 the charts on FDA's website for 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. Analysis may be necessary to verify the level of the nutrient and a physical sample must be collected.

i. Collect a sample of any product that is labeled with an unqualified claim under Area of Emphasis No. 4.

ii. 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.

iii. 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.

iv. For import samples, only 12 retail packages are to be collected. Collect one package from 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.

v. Prepare a Collection Report (C/R) for each sample collected and mark as "Official" in the **Sample Type** field.

vi. 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."

c) **Area of Emphasis No. 10**

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).** New regulations at 21 CFR 189.5(c), include record keeping that demonstrate that products are not made with prohibited materials. Records must be maintained for 2 years and FDA must be allowed to inspect and copy them. These requirements became effective on January 9, 2007.

i. The EIR and all supporting documents (see Part III, page 9) must be mailed to the General Program contact immediately following completion of the inspection.

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

d) **Area of Emphasis No. 11**

The February 11, 2004 final rule declaring dietary supplements that contain ephedrine alkaloids adulterated remains in force.

i. For products that appear to contain a source of ephedrine alkaloids collect an official sample consisting of three retail units of each product.

ii. Collect a maximum of 3-5 samples each consisting of a different lot number. Do not commingle lots.

iii. Include information on the size of each lot sampled on the collection report.

iv. If the product is manufactured or warehoused at another location, this must be indicated on the collection report.

2) Surveillance Samples

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 district 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 district 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) 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 ATTACHMENT B 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.**

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. The sample must represent a single lot code. Contact Atlanta Center for Nutrient Analysis (ACNA) at (404) 253-1181 if necessary if there are any additional questions on sample size.

E. **Shipment of Samples for Nutrient Analysis**

Ship all samples to:

Southeast Regional Laboratory (HFR-SE680)
Atlanta Center for Nutrient Analysis (ACNA)
60 Eighth Street, N.E.
Atlanta, GA 30309
(404) 253-1181

NOTE: Notify ACNA by phone when compliance samples are collected and provide all shipping information so that arrangements can be made to expedite sample analysis.

Fully explain the reason(s) for collection on the Collection Report (C/R). For compliance samples, this would include a brief description of the inspectional observation(s) which resulted in collection, e.g., improper enrichment procedures, improper storage of raw material. For samples collected for health claim or nutrient content claim analysis, i.e., Area of Emphasis 4, indicate the suspect nutrient forming the basis for the health claim or nutrient content claim. Send a copy of the C/R to ACNA along with the sample.

NOTE: For compliance samples, make certain that the C/Rs are flagged "COMPLIANCE SAMPLE - ANALYZE UPON RECEIPT."

Compliance samples should be shipped to ACNA using overnight delivery service.

F. **Documentary/Paper Samples for Label Review**

All documentary (in OASIS paper) samples collected under Areas of Emphasis 1, 2, 3, 5, 6, 7, 8, or 9 and those containing suspected new dietary ingredients should be forwarded to the district's compliance branch for a label review and sample classification. Label reviews must be reported into FACTS and each sample that undergoes a label review must be classified.

G. **Shipment of Samples for Ephedrine Alkaloid Analysis**

Arkansas Regional Laboratory (ARL)
Food and Drug Administration
3900 NCTR Road, Bldg., 26
Jefferson, AR 72079-9502
Phone 870-543-4099

H. **Hardcopy Reporting to CFSAN**

For NAI and VAI inspections, within 30 days after completion of each inspection, notify CFSAN via e-mail to ~~Brenda.Aloi@fda.hhs.gov~~ mallory.kelly@fda.hhs.gov that the EIR is completed in Turbo EIR. Provide the firm name, FEI and the inspection completion date in the e-mail.

For OAI inspections, prepare and submit a recommendation in the Compliance Management Services (CMS) in accordance with the Regulatory Procedures Manual (RPM) timeframes.

I. **FACTS/OASIS Reporting**

Enter each establishment inspection report into Turbo EIR. Citations to the applicable sections of the new Dietary Supplement GMPs have been established and loaded into Turbo EIR for preparation of FDA 483 "Notice of Inspectional Observations." There are also citations related to the adverse event reporting requirements in Turbo EIR.

PACS

21008 Inspections conducted at firms not subject to Part 111, all sample collections and analyses, and all import operations.
21008A Inspections at firms subject to Part 111 including foreign firms.
21R839 All health fraud related activities.

When reporting import operations, time spent reviewing import labels that does not result in a sample collection must be reported as an import field exam (OASIS #23). Time spent collecting labels, records, or other documentation for submission to the Compliance Branch for review is to be reported as an import sample collection paper (OASIS #41). Do not include time spent reviewing the import label under operation #41. Time spent reviewing the label will be included as OASIS #27 and reported along with the compliance review time as OASIS #43.

PART IV - ANALYTICAL

A. Nutrient Analysis

Atlanta Center for Nutrient Analysis (ACNA), HFR-SE680.

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.

For the reviewer's convenience, a model review format is provided as ATTACHMENT C. Use ATTACHMENT C for recording observations only DO NOT submit to the Center.

2. **Analyses**

a) Do not perform nutrient analyses on samples containing more than one manufacturing lot code. Notify the collecting district 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. 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, or Vitamin C.

- 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.

c) 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. For tablets, capsules, or bars, composite a minimum of 12 servings, 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 or National Formulary, as applicable and appropriate. Use of methods contained in one of these compendials 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.

d) 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 B. 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 the current edition of the AOAC, Ch. 45, Method 985.29, 991.42, 991.43, or 993.19 whichever is appropriate.

3. **Analytical Reporting**

ACNA will report all samples classified as class 3 based on nutrient analyses to the compliance branch of the collecting district for appropriate regulatory follow-up.

Report all analytical results into FACTS using Problem Area Flag “NIF” (Infant Formula). The use of PAF "NIF" is necessary so that the following additional analytical information, not captured in PAF "NIS" will be entered:

a) the complete product name, including brand name, in the product description field;

b) the use by date; and

c) the lot or other batch identification number.

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

B. Ephedrine Alkaloid Analysis

Arkansas Regional Laboratory (ARL), HFR-SW500

1. ARL will use the following published method for original analysis of each sample: 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.” Each sample should be tested for the six ephedrine alkaloids (EA) included in the method.

2. No further testing is necessary for samples testing negative using the above HPLC-UV method. Conduct a check analysis using either the HPLC-UV method above or the LC/MS method noted below depending on the laboratory set-up. Both of these methods are suitable for quantitative check analsis.

3. Confirmatory analysis must be done on each positive sample using the following method: 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.

4. Analyze each sample on a composite basis only, e.g., do not analyze individual tablets or capsules. For each ephedrine alkaloid (EA) found in a sample:

   a) Determine the average weight for hard tablets and capsules and the average capsule content weight for soft capsules;
   b) Show the calculation and report the concentration (ug/g, ug/mL) for individual and total EAs for the composite as directed in the methodology;
   c) Show the calculation and report the EA level as mg per unit dose;
   d) Calculate and report the total EA level as mg per serving size as directed on the label;
   e) Show the calculation and report daily total EA intake based in milligrams (mg) on daily serving size as directed on the label (if available).

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

6. Use PAC 21008 PAF Narrative Field (NAR) to report the daily dosage level of ephedrine alkaloids found in the product.

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

PART V - REGULATORY/ADMINISTRATIVE FOLLOW-UP

Regulatory recommendations must be submitted to the Division of Enforcement via electronic copy (e.g., doc, pdf files, etc..) via the "Mission Accomplishment and Regulatory Compliance Services-Compliance Management Services" (MARCS-CMS) link located on Inside FDA's IT Application Page under ORA Applications.

Include a good, legible scanned or digital photo copy of the product label with each recommendation. If the label cannot be captured electronically, Districts should submit an original label to the Division of Enforcement. When charges are based on analytical results, each recommendation must include a copy of the collection report, an original product label, all analyst worksheets, and other pertinent information, such as documentation of method performance for all "Non-Official" methods utilized.

Note: Warning Letters and seizure recommendations should not include labeling deviations that are not of regulatory significance. Questions about the significance of labeling deviations should be referred to the Regulatory Contact listed in Part VI of this program.

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

A. GMP Violations

Under section 402(g)(1) of the Federal Food, Drug and Cosmetic Act (the Act), a dietary supplement is adulterated if it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations.

Major deviations from cGMPs include:

- Lack of master manufacturing records or significant requirements not included;
- Lack of finished product release criteria or failure to test (all or subset of finished batches) or meet finished product release criteria critical to product safety and quality;
- For significant dietary ingredients, e.g. those that make up the bulk of the product, failure to establish specifications for incoming material or failure to conduct identity testing;
- No quality control review procedures or significant quality control procedures not implemented;
- No batch records;
- Significant physical plant deficiencies.

Districts should prepare and submit to CFSAN/Division of Enforcement (DE)/Labeling Compliance Team (LCT) a Warning Letter recommendation for any firm with any of the above deviations.

Specimen charge:

"The article is adulterated within the meaning of Section 402(g)(1) of the Federal Food, Drug and Cosmetic Act (the Act) [21 U.S.C. § 343(g)(1)] because it has been prepared, packed, or held under conditions that do not meet the current good manufacturing practice

regulations for dietary supplements in 21 CFR Part 111."

For other significant deviations, districts should submit a recommendation for an untitled letter. Other less significant deviations from cGMPs should be noted on the FDA-483 and discussed with firm management at the close of the inspection.

B. Label Violations

District 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 D for standard language to be included in Warning Letters.

DOMESTIC PRODUCTS

1. Areas of Emphasis Nos. 1 and 6

a. Districts may consider issuing Warning Letters directly to firms whose product(s):

- fail to bear nutrition labeling and are not exempt; or
- are in solid oral dosage form and contain added iron or iron salts but do not bear a warning statement.

b. This direct reference authority applies only to product labels that fall into one or more of the above areas, but conform to all the other areas of emphasis including providing mandatory labeling information. Regulatory recommendations against product labels that do not conform to one of the other areas of emphasis noted below must be handled as indicated below under 2.

c. The Office of Nutrition, Labeling, and Dietary Supplements (HFS-810) must be included on the distribution list for these letters. A copy of these direct reference Warning Letters must be uploaded into the MARCS-CMS case file.

2. Areas of Emphasis 2, 3, 5, 7, 8 and 9

a. Districts should prepare Warning Letter recommendations against firms whose product(s):

- fail 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;
- 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.

Enforcement actions will be considered against products that bear egregious disease claims or structure/function claims that may be unsubstantiated. Products that bear inappropriate disease claims or that appear to bear egregiously false or misleading structure/function claims should be referred to CFSAN for evaluation.

- bear nutrition labeling ("Supplement Facts" panel) with significant format deviations;
- uses the term "ginseng" to describe the product or an ingredient and the product or ingredient is not an herb or herbal ingredient derived from a plant classified within the genus "Panax";
- fail to disclose a required major food allergen;
- fail to bear other mandatory nutrition labeling;

IMPORTED PRODUCTS

a. When an import sample fails to conform to the criteria listed in Areas of Emphasis 1, 2, 3, 5, 6, 7, 8 and 9 districts should consider detaining the entry. In addition, the district should submit a Recommendation For Detention Without Physical Examination (DWPE) to ORA/DIOP (HFC-170). Follow the criteria stated in the Regulatory Procedures Manual (RPM) Chapter 9, Subchapter—Automatic Detentions-to place a firm/product on Import Alert 99-20 – "Detention Without Physical Examination of Imported Food Products Due to NLEA Violations"

b. An **ORIGINAL** or quality copy of the label **MUST** be included in the package submitted to the ORA/DIOP for review. The recommendation must be submitted through MARCS-CMS.

C. Nutrient Analysis

1. Conditions of Concern

- The analysis supports the fact that the product does not qualify to make the health claim or nutrient content claim contained on the product label (Area of Emphasis No. 4), or

- The sample does not comply with the requirement found at 21 CFR 101.9(g)(4) regarding nutrients that are not present in the declared amounts.

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

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

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; and

- 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.

3. Recommendations for Follow-up

Follow the criteria below in recommending regulatory follow-up:

a) Compliance Samples

- If the domestic sample was collected exactly as required in 21 CFR 101.36(f)(1) and a seizable size lot 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 seizable size lot is not available, recommend issuance of a Warning Letter.

b) Surveillance Samples

Warning Letter recommendations should be prepared and forwarded for surveillance samples meeting the criteria in B. 1. above.

c) Import Samples.

For import samples that meet the criteria in B. 1. above, submit a recommendation for a new import alert for detention without physical examination (DWPE) to ORA/DIOP, in MARCS-CMS. Shipments of the same product offered for entry into any FDA district port should be handled in accordance with the guidance provided in the new import alert.

Each recommendation must include a copy of entry documents (CBP Form 3461 and/or CBP Form 7501, invoices, bills of lading/air waybills), the collection report, an original product label (or quality copy), all analyst worksheets, and other pertinent information, such as documentation of method performance for all "Non-Official" methods utilized.

Districts should submit recommendations for District Requested Criteria (DRC) to DIOP Systems Branch (email: ORA HQ DIOP Systems Branch) with a copy to the Director, DIOP Operations and Policy Branch. The DRC will set criteria in OASIS to cover importations of product during the import alert revision process.

D. 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 district must forward the EIR and all documentation via CMS to CFSAN for further regulatory consideration.

1) A bovine-derived ingredient is a prohibited cattle material under 21 CFR 189.5(a) if it is a specified risk material that has not been inspected and passed for human consumption by a competent authority or is otherwise a prohibited material under 21 CFR 189.5(a). Affirmative evidence of the use of prohibited cattle material must be collected.

2) If the firm is using bovine-derived ingredients, they must have records to show that the food is not manufactured from, processed with, or does not otherwise contain prohibited cattle materials (21 CFR 189.5(c)). Documentation of the lack of these records must be collected.

3) Under the new dietary supplement CGMP regulations, firms must establish specifications for animal-derived ingredients that are necessary to ensure the quality of the dietary supplement. Firms must also take necessary actions to determine that specifications are met. If such specifications are not established or met, collect adequate documentation of the deficiency.

E. Ephedrine Alkaloid Containing Dietary Supplements

The Center is prepared to move forward quickly against significant volumes of 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.

In the absence of voluntary actions, compliance branches should discuss the findings with the CFSAN compliance/enforcement contact. If appropriate, districts should submit seizure recommendations by electronic copy (e.g. doc, pdf files, etc.) via the MARCS-CMS link.

Refer to Section 6-1 of the Regulatory Procedures Manual (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:

District compliance branches must request trace back investigation of finished product and suppliers for any product that tests positive for ephedrine alkaloids. If the product or raw material is of import origin, submit the relevant information on country, port of entry, shipper, importer, etc. to ORA/DIOP through MARCS-CMS.

F. Adverse Event Reporting Requirements

Section 761 of the Act applies to the requirements for adverse event reporting for dietary supplements. FDA's website includes finalized guidance for industry.

1. Violations of reporting and recordkeeping requirements.

Firms are required by statute to submit to FDA all reports of serious 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 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 District should submit a Warning Letter recommendation. If the firm has performed the requirements but the documentation or actions appear to be inadequate, the District may consider submitting an Untitled Letter recommendation.

2. Label Violations

Although the requirements of section 403(y) of the Act apply to all dietary supplements labeled on or after December 22, 2007, FDA intends to exercise enforcement discretion for the requirement to include a domestic address or domestic phone number through which the responsible person may receive a report of a serious adverse event with a dietary supplement until September 30, 2010.

FDA finalized guidance on the labeling requirements of Section 403(y) in September 2009. The final labeling guidance can be accessed on FDA's internet website. Because firms did not have the benefit of FDA guidance on how to comply with the new requirements when they went into effect, FDA has determined that it will use enforcement discretion until September 30, 2010 to afford firms ample opportunity to bring the labeling of their products into compliance. Products labeled prior to this date do not have to be re-labeled if they do not comply.

PART VI - ATTACHMENTS AND CONTACTS

ATTACHMENTS

ATTACHMENT A – Exemptions from Nutrition Labeling (“Supplement Facts” Panel)
ATTACHMENT B – Table of Essential Nutrients and their Established RDI or DRV Levels
ATTACHMENT C - Model Nutrition Labeling ("Supplement Facts" Panel) Review Format
ATTACHMENT D - Standard Language for Warning Letters
Attachment E – List of Botanicals for Priority Coverage During Inspections

REFERENCES

For Areas of Emphasis

No. 1—Products that fail to bear nutrition labeling--See 21 CFR 101.36, including 101.36(h)(1), (2), and (3) and firms that have filed for an exemption from nutrition labeling
No. 2—Products that fail to bear an appropriate statement of identity--See 21 CFR 101.3(g) and industry guidance on statement of identity and ingredient labeling
No. 3—Products that bear health claims or nutrient content claims—See Claims that Can be Made for Conventional Foods and Dietary Supplements
No. 4—-See 21 CFR 101.13 and 101.14 and Qualified Nutrient Content and Health Claims
No. 5—Products bearing significant “Supplement Facts” panel deviations--See 21 CFR 101.36 and Chapter IV of the Dietary Supplement Labeling Guide
No. 6—See 21 CFR 101.17(e)(1) and Guidance for Industry: Iron Containing Supplements and Drugs
No. 7—Products labeled with “ginseng”--See Section 403(u) of the Act and 21 CFR 101.4(h)
No. 8-Products that fail to declare a major food allergen--See Section 403(w) of the Act and the Food Allergen Labeling and Consumer Protection Act of 2004
No. 9-Products that fail to bear other mandatory labeling information--See Dietary Supplement Labeling Guide
No. 10-Failure to maintain records for cattle derived material--See 21 CFR 189.5
No. 11-Products that appear to contain a source of ephedrine alkaloids--See 21 CFR 119.1

CONTACTS

1. Method Inquiries

   Dr. Jeanne Rader CFSAN/OCD/DBC,(240) 402-1786 for all questions except those related to metals/minerals.

   Metals/Minerals--William Mindak,(240) 402-2005 or Steven Capar,(240) 402-2003, CFSAN/OCD/ORS/DBC.

   George Salem, ORA/Division of Field Science,(301) 827-1031.

2. Inspectional Inquiries

Norman Fogg, ORA/Division of Field Investigations,(301) 827-5645.

Domestic-Import and Import Sampling, ORA/DIOP.

3. Program Contact

Mallory Kelly, CFSAN/OC/DFPG/Field Programs Branch,
(240) 402-2401, Fax (301) 436-2657.

4. Compliance/Enforcement Contact

Quyen Tien 215-717-3705 CFSAN/OC/DE/Labeling and Dietary Compliance Team

5. Low Volume/Small Business Exemption Questions

Felicia Billingslea, CFSAN/ONLDS (240) 402-2371

6. Regulatory Policy Questions Including New Dietary Ingredients

Daniel Fabricant CFSAN/ONLDS (240) 402-2375 or Corey Hilmas CFSAN/ONLDS
(240) 402-2177

PART VII - CENTER RESPONSIBILITY

The Director, Office of Nutrition Labeling and Dietary Supplements (ONLDS) will prepare periodic formal evaluations of this compliance program. When completed and cleared, the evaluation will be available for Agency personnel on FDA's intranet website at: http://inside.fda.gov/ProgramsInitiatives/Food/FieldPrograms/ucm015758.html. Additionally, the evaluation when completed will appear on this website location.

EXEMPTIONS FROM NUTRITION LABELING ("SUPPLEMENT FACTS" PANEL)

A dietary supplement is not required to have a "Supplement Facts" panel 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 ONPLDS; or

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.

TABLE OF ESSENTIAL NUTRIENTS AND THEIR ESTABLISHED REFERENCE DAILY INTAKE OR DAILY REFERENCE VALUE

Nutrient	RDI or DRV
Protein	50 grams
Fiber	25 grams
Vitamin A	5,000 international units
Vitamin C	60 milligrams
Calcium	1 gram
Iron	18 milligrams
Vitamin D	400 international units
Vitamin E	30 international units
Vitamin K	80 micrograms
Thiamin	1.5 milligrams
Riboflavin	1.7 milligrams
Niacin	20 milligrams
Vitamin B6	2.0 milligrams
Folate	400 micrograms
Vitamin B12	6.0 micrograms
Biotin	300 micrograms
Pantothenic acid	10 milligrams
Phosphorus	1000 milligrams
Magnesium	400 milligrams
Zinc	15 milligrams
Iodine	150 micrograms
Copper	2.0 milligrams
Potassium	3,500 milligrams
Chromium	120 micrograms
Molybdenum	75 micrograms
Chloride	3,400 milligrams

RDI and DRV for Adults and Children over 4 Years of Age

Model Nutrition Labeling ("Supplement Facts" Panel) Review Format

Food_____ Sample #_____

Mark with: + = Information present and correct on label
- = Information present and incorrect on label
O = Information missing from label

Label Format

1. Type size _____
2. Upper & lower case letters _____
3. Bars and hairlines present _____
4. Good color contrast _____
5. Bolding on primary nutrients and % DVs _____
6. Headings: Nutrition Facts, Amt/Serving, % DV_____
7. Footnotes _____
8. Simplified or shortened format (qualifies? correct?) _____
9. Serving size _____
10. Servings/container _____

Label Content

1. Calories _____
2. Calories from fat _____
3. Total fat (g & % DV) _____
4. Saturated fat (g & % DV) _____
5. Cholesterol (mg & % DV) _____
6. Sodium (mg & % DV) _____
7. Total carbohydrate (g & % DV) _____
8. Dietary fiber (g & % DV) _____
9. Sugars (g) _____
10. Protein (g) _____
11. Vitamin A (% DV) _____
12. Vitamin C (% DV) _____
13. Calcium (% DV) _____
14. Iron (% DV) _____
15. Voluntary additional nutrients _____
16. Order of listed nutrients _____

Use this form for recording observations only, do not submit to CFSAN

STANDARD LANGUAGE FOR WARNING LETTERS
IN AREAS OF EMPHASIS

Follow the format in Chapter 4 of the current edition of the Regulatory Procedures Manual (RPM). Incorporate one or more of the following paragraphs as appropriate. This is the agreed upon language for use in proposed Warning Letters.

Area of Emphasis No. 1

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" panel), which is required under 21 CFR 101.36, and is not exempt from this requirement.

Area of Emphasis No. 2

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)).

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.

Note: Area of Emphasis No. 4 is not included. Refer to Part V for instructions on follow-up to nutrient deficiencies.

Area of Emphasis No. 5

The product is misbranded within the meaning of section 403(q) of the Act in that the label fails to bear nutrition information as required by 21 CFR 101.36.

STANDARD LANGUAGE FOR WARNING LETTERS
IN AREAS OF EMPHASIS

Area of Emphasis No. 6

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)).

Area of Emphasis No. 7

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. 8

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

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

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

Guidance on the allergen labeling requirements in section 403(w) may be found on FDA's website at www.fda.gov.

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. 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 statement of identity:
The product is misbranded under section 403(s)(2)(B) of the Act because the label fails to identify the product using the term "dietary supplement."

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 adulterated under section 402(a)(4) of the Act because it was manufactured from, processed with, or otherwise contains material from cattle and the firm does not have records sufficient to demonstrate that the food is not manufactured from, processed with, or does not otherwise contain, prohibited cattle materials. 21 CFR 189.5(d).

Area of Emphasis No. 11

The product is adulterated under section 402(f)(1)(A) of the Act because it contains ephedrine alklaloids 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).

NOTE: Under section 403(r)(6) of the Act, a dietary supplement may bear certain claims, generally called "structure/function claims," on its label or in its labeling provided that the firm has substantiation that the claim is truthful and not misleading; the firm has notified FDA within 30 days of marketing the product bearing the claim; and the claim includes a mandatory disclaimer.

The Agency will consider, on a case-by-case basis, enforcement actions against products that bear egregious disease claims or that may be unsubstantiated and false and misleading. Investigators should review claims made for dietary supplements in labels and labeling. Products that bear inappropriate disease claims or that appear to bear egregiously false and misleading claims should be referred to CFSAN, Division of Enforcement (HFS-605) for evaluation.

The preamble to the final rule that published on January 6, 2000 (65 FR 1000)—Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, provides important background and rational for the Agency's policies related to structure/function and disease claims issue. In addition to the preamble discussion, the Agency issued a guidance document on January 9, 2002, which provides additional information regarding structure/function and disease claims entitled "Guidance for Industry, Structure/Function Claims, Small Entity Compliance Guide." The guidance document complements, rather than substitutes for, the final rule and is available on FDA's internet website. Districts may want to refer to this document for industry guidance prepared in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act. This guidance restates in plan language the legal requirements set forth in the January 6, 2000 regulation concerning labeling claims for dietary supplements.

Botanicals to Consider When Deciding Product Coverage

Acacia rigidula: (Other common names: Black brush or Chaparro Prieto)
Scientific Name: *Acacia rigidula Benth.*
Interest: New dietary ingredient for which a notice is required; possible toxicity issue

Caralluma fimbriata (Other common names: Indian Hoodia ; Caralluma cactus)
Scientific Name: *Caralluma fimbriata , Caralluma adscendens*
Interest: Identity; substitution by other ingredients

Hoodia gordonii: (Other common names: African Hoodia cactus; Bokhorings; Bushmen's hat)
Scientific Name: *Hoodia gordonii*
Interest: Identity; substitution by other ingredients

Withania somnifera (Other common names: Indian ginseng, Ashwagandha, Winter Cherry)
Scientific Name: *Withania somnifera*
Interest: Identity and contamination (origin in third world countries)

Bacopa monnieri (Other common names: Brahmi, Water hyssop)
Scientific Name: *Bacopa monnieri*
Interest: Identity and contamination (origin in third world countries)

Black cohosh (Other common names: black snakeroot, macrotys, bugbane, bugwort, rattleroot, rattleweed)
Scientific Name: *Actaea racemosa, Cimicifuga racemosa*
Interest: Identity. (substituted for with other plants; economic adult.)

Scutellaria: (Other common names: skullcap, mad dog)
Scientific name: *Scutellaria lateriflora L.*
Interest: Identity (substituted for with other plants; economic adult.)

Memordica Chrantia (Other common names: bitter Guard/bitter melon)
Scientific Name: *Memordica Charantia*
Interest: Identity and contamination (origin in third world countries)

Milk thistle
Scientific Name: *Silybum marianum* (L.) Gaertn.
Interest: Identity and contamination. (origin in third world countries)

Goldenseal
Scientific Name: *Hydrastis canadensis* L.
Interest: Substitution by, or contamination with**,** Berberis/Mahonia species, *Coptis groenlandica* L. *C. trifolia* (L.) Salisb; or *Xathorhiza simplicissima* Marshall, all of which shares a yellow color (Wendy) (econ. adulteration)

Akebia (Three-leaf akebia)
Scientific name: *Akebia trifoliate* (Thunb.) Koidz.
Interest: Substitution by, or contamination with, Aristolochia spp. (which is toxic)

Stephania
Scientific name: *Stephania tetrandra* S. Moore
Interest: Substitution by, or contamination with, Aristolochia spp. (which is toxic)

Plantain:
Scientific Name: *Plantago major L.*
Interest: Substitution by, or contamination with, Digitalis lanata (which is a toxic plant)