

## Food

### **Guidance for Industry: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Small Entity Compliance Guide**

*Contains Nonbinding Recommendations*

December 2010

#### **Small Entity Compliance Guide**

You may submit either electronic or written comments regarding this guidance at any time. Submit electronic comments to <http://www.regulations.gov><sup>1</sup>. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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#### **U.S. Department of Health and Human Services Food and Drug Administration Center for Food Safety and Applied Nutrition December 2010**

*Contains Nonbinding Recommendations*

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## **Guidance for Industry<sup>1</sup>**

### **Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements Small Entity Compliance Guide**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

## **I. Introduction**

On June 25, 2007, FDA published in the *Federal Register* a final rule that established a regulation (21 CFR part 111) entitled Current Good Manufacturing Practice (CGMP) In Manufacturing, Packaging, Labeling, Or Holding Operations For Dietary Supplements (72 FR 34752). The Dietary Supplement (DS) CGMP rule in 21 CFR part 111 (“the DS CGMP rule”) requires persons who manufacture, package, label, or hold a dietary supplement to establish and follow current good manufacturing practice to ensure the quality of the dietary supplement and to ensure that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

In the same issue of the *Federal Register* (72 FR 34959), FDA also issued an interim final rule (the identity testing interim final rule) setting forth a procedure for requesting an exemption from a requirement of the DS CGMP rule for the manufacturer to conduct at least one appropriate test or examination to verify the identity of any dietary ingredient that is a component of a dietary supplement. The provisions of the identity testing interim final rule have the full force of law, but FDA provided a 90-day comment period on those provisions through September 24, 2007. On September 17, 2007, FDA published a notice in the *Federal Register* to extend the comment period to October 24, 2007.

The DS CGMP rule and the identity testing interim final rule were effective as of August 24, 2007. The compliance dates are described below.

FDA has prepared this Small Entity Compliance Guide in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). This guidance document restates in plain language the legal requirements set forth in the DS CGMP rule (21 CFR part 111). The DS CGMP rule is binding and has the full force and effect of law.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead,

guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. Discussion

### A. Compliance Dates for the Dietary Supplement Current Good Manufacturing Practice Rule (DS CGMP Rule) and the Interim Final Rule

#### 1. What were the compliance dates for the DS CGMP rule?

As shown in Table 1, the compliance dates were based on how many full-time equivalent employees (FTEs) you employ.

**Table 1**

#### **Compliance Dates Based on the Size of Your Organization**

<b>If you employ ...</b>	<b>The DS CGMP rule required you to comply by ...</b>
500 or more FTEs	June 25, 2008
At least 20 but fewer than 500 FTEs	June 25, 2009
Fewer than 20 FTEs	June 25, 2010

### B. Organization of the DS CGMP Rule

#### 1. How is the DS CGMP rule organized?

The DS CGMP rule is organized as a series of "subparts," which each cover a different aspect of current good manufacturing practice. We list these subparts in Table 2.

**Table 2**

#### **Subparts of the DS CGMP Rule**

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

## III. Subpart A – General Provisions

### A. Coverage of the DS CGMP Rule

#### 1. Who is subject to the DS CGMP rule?

You are subject to the DS CGMP rule if you manufacture, package, label, or hold a dietary supplement. (21 CFR 111.1(a))

In our answers to questions in sections III.A, III.B, III.C and XIX of this document, we address some specific examples of firms who do, or do not, fall within the coverage of the DS CGMP rule.

#### 2. Am I subject to the DS CGMP rule if I am a foreign firm?

Yes. The DS CGMP rule applies to you if you manufacture, package, label, or hold a dietary supplement imported or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(21 CFR 111.1(a)(2))

#### 3. Am I subject to the DS CGMP rule if my product is sold only within my state?

You may be subject to the DS CGMP rule for products sold only within your state. FDA may consider its jurisdiction over such products under the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, or both, depending on the circumstances of the situation.

(72 FR 34752 at 34785)

4. **Am I subject to the holding requirements established in the DS CGMP rule if I am a retailer who is holding dietary supplements at a retail establishment for the sole purpose of direct retail sale to individual consumers?**

No. Importantly, a retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers.

(21 CFR 111.1(b); 72 FR 34792)

5. **Am I subject to the holding requirements established in the DS CGMP rule if I am a retailer who operates a warehouse or storage facility?**

Yes. The "retail exemption" does not apply to you, because a retail establishment does not include a warehouse or other storage facility for a retailer or a warehouse or other storage facility that sells directly to individual consumers (21 CFR 111.1(b); 72 FR 34752 at 34792).

6. **Do the requirements of the DS CGMP rule apply to all types of dietary supplements (e.g., for botanical dietary supplements and for vitamin/mineral dietary supplements)?**

Yes.

(72 FR 34752 at 34913)

**B. How the DS CGMP Rule Applies to Specific Types of Operations**

1. **Am I subject to the DS CGMP rule if I package, label, or distribute a dietary supplement manufactured by another firm?**

Yes. The DS CGMP rule requires you to comply with those provisions directly applicable to the operations you perform.

For example, if you are a labeler, the DS CGMP rule:

- Requires you to comply with the requirement in 21 CFR 111.255 to establish a batch production record;
- Requires you to comply with other applicable requirements, such as requirements for personnel, physical plant and grounds, equipment and utensils, and holding operations;
- Does not require you to comply with the requirement of 21 CFR 111.260(e) to include the identity and weight or measure of each component used, because you would be starting from packages that already had been filled rather than from individual components.

As another example, if you are a distributor who purchases a packaged and labeled dietary supplement and then holds the product in a warehouse for distribution to another physical location, the DS CGMP rule

- Requires you to comply with requirements for holding and distributing; and
- Requires you to comply with other applicable requirements, such as requirements for personnel, the physical plant and grounds.

(21 CFR 111.1(a) and (a)(1); 72 FR 34752 at 34790 and 34886)

2. **Am I subject to the DS CGMP rule if I manufacture a dietary ingredient (or a "pre-mix" of dietary ingredients) used by another manufacturer to make a dietary supplement?**

Whether you are subject to the DS CGMP rule depends on the totality of your business operation (72 FR 34752 at 34791). For example:

- You are not subject to the DS CGMP rule if your only customers are other manufacturers who further process the dietary ingredient to make a dietary supplement (72 FR 34752 at 34791). However, we encourage firms who only supply dietary ingredients to other firms for further processing as part of the manufacture of a dietary supplement to adhere to the applicable provisions established in the DS CGMP rule that apply to their operations (72 FR 34752 at 34805).
- You would be subject to the DS CGMP rule if you sell a dietary ingredient to a firm who simply packages the dietary ingredient for sale as a dietary supplement, or labels your packaged dietary ingredient for sale as a dietary supplement, because in this circumstance you are manufacturing a dietary supplement that another firm is simply packaging or labeling without further processing into a dietary supplement (72 FR 34752 at 34791). In other words, you would have acted as a manufacturer whose finished product is simply repackaged or relabeled.
- You would be subject to the DS CGMP rule if you supply a dietary ingredient directly to consumers (72 FR 34752 at 34791); you would be considered a dietary supplement manufacturer in such a situation.

3. **Am I subject to the DS CGMP rule if I manufacture a dietary supplement that is packaged or labeled by another firm – e.g., if I sell my dietary supplement to another firm for packaging and labeling and do not sell my dietary supplement directly to consumers?**

Yes. The DS CGMP rule requires you to comply with those provisions directly applicable to the operations

you perform (21 CFR 111.1(a)(1); 72 FR 34752 at 34790). For example, you are required to make and keep records of product distribution (21 CFR 111.475).

4. **Am I subject to the DS CGMP rule if I harvest, store, or distribute raw agricultural commodities that will be incorporated into a dietary supplement by others?**

No. If you simply supply a raw agricultural commodity that another person will process into a dietary supplement, you are not considered to be engaging in the manufacture, packing, labeling, or holding of a dietary supplement. However, if you simply supply bulk material to someone who packages it in smaller packages or you sell agricultural commodities to the consumer as a dietary supplement, you would be considered the manufacturer.

(21 CFR 111.1(a); 72 FR 34752 at 34792)

5. **Am I responsible for the oversight of a packager/labeler if I am a manufacturer and I sell my dietary supplement to the packager/labeler?**

No. You would not be responsible for the oversight of the packager/labeler, because:

- The packager/labeler is not under your control; and
- The packager/labeler (rather than you) has control over the release of the packaged and labeled dietary supplement

(72 FR 34752 at 34790)

6. **When am I subject to the specific requirements applying to product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?**

You are subject to the specific requirements (such as those in 21 CFR 111.70(f), 111.75(e), 111.127(a) and (b), and 111.165) applying to product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) if you will distribute the dietary supplement that you package or label rather than return it to the person who supplied it to you. This means that you are subject to those specific requirements if the product that you will package or label has left the control of the firm who supplied it to you (e.g., because you purchased the product).

(72 FR 34752 at 34844)

7. **When am I not subject to the specific requirements applying to product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)?**

You are not subject to the specific requirements (such as those in 21 CFR 111.70(f), 111.75(e), 111.127(a) and (b), and 111.165) applying to product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) if you package or label a dietary supplement under contract to a firm who supplied the product to you, and then return it to that firm rather than distribute it yourself. For the purposes of the DS CGMP rule, this situation is no different than a situation in which the packaging or labeling of the dietary supplement is done by the firm who manufactured the product, because the product remains under the control of the firm who arranged for your services under contract.

(72 FR 34752 at 34844)

8. **Am I subject to the DS CGMP rule if I am a practitioner (such as an herbalist, acupuncturist, naturopath, or other related health care provider)?**

Yes. Practitioners such as herbalists, acupuncturists, naturopaths, and other related health care providers are subject to the DS CGMP rule. However, we believe that it would be appropriate to consider the exercise of our enforcement discretion in certain circumstances (see example which follows in the next question).

(72 FR 34752 at 34793)

9. **How does FDA expect to apply the DS CGMP rule to practitioners?**

FDA expects to exercise enforcement discretion, on a case-by-case basis, in determining whether to apply the DS CGMP rule to practitioners such as herbalists, acupuncturists, naturopaths, and other related health care providers. For example:

- We expect to exercise discretion in the case of a one-on-one consultation by a practitioner who is adequately trained in his or her profession. We believe such a case may not necessitate the same types of controls as we established in the DS CGMP rule for manufacturing activities on a larger scale. Such a practitioner may make some formulations in advance of the consultation and still make the formulations in very limited quantities for the individual client.
- We are not considering exercising our enforcement discretion with respect to practitioners who prepare batches of dietary supplements and sell them to individual consumers without determining whether the dietary supplement is appropriate for each consumer's needs in a one-on-one personal consultation.

- We are not considering exercising our enforcement discretion with respect to practitioners who prepare batches of a dietary supplement for which there is a known or suspected safety concern.

We do not expect the number of practitioners subject to the consideration of our enforcement discretion to be very large. Many products manufactured by practitioners would not necessarily be considered to be dietary supplements (e.g., certain products used by traditional Asian medicine practitioners).

(72 FR 34752 at 34793)

### C. How the DS CGMP Rule Applies to Contractors

#### 1. Does the DS CGMP rule apply to a contractor who provides a service to a firm who is subject to the DS CGMP rule?

Yes. Contractors who provide a particular service (such as packaging, labeling or both packaging and labeling) to a firm who is subject to the DS CGMP rule must comply with those regulations directly applicable to the operations they perform for the firm who contracted with them (72 FR 34752 at 34790). For example, if a contractor is a labeler, the DS CGMP rule:

- Requires the contractor to comply with the requirement in 21 CFR 111.255 to establish a batch production record;
- Requires the contractor to comply with other applicable requirements, such as requirements for personnel, physical plant and grounds, equipment and utensils, and holding operations;
- Does not require the contractor to comply with the requirement of 21 CFR 111.260(e) to include the identity and weight or measure of each component used, because the contractor would be starting from packages that already had been filled rather than from individual components.

#### 2. What are some examples of how the requirements of the DS CGMP rule apply under contractual relationships?

Below, we provide three examples of how the requirements of the DS CGMP rule apply under contractual relationships. Importantly, it is not practical to list all possible contractual relationships that persons may enter into in the manufacture of a dietary supplement, or to list all businesses or practices that may be subject to the requirements of the DS CGMP rule.

- **Example 1.** A manufacturer who contracts with a person to do packaging and labeling, but who later distributes the packaged and labeled product, is ultimately responsible for the dietary supplement it releases for distribution. The manufacturer would be responsible for the CGMP requirements for the operations it performs, including those related to the release of the product for distribution. For example, the manufacturer would determine whether the packaged and labeled dietary supplement it receives from the packager/labeler conforms to applicable specifications (21 CFR 111.127(d)), and is responsible for approving the release of the packaged and labeled dietary supplement for distribution (21 CFR 111.127(h)). Although the manufacturer is not performing the specific activities related to the packaging and labeling operations done by another person, the manufacturer has an obligation to know what and how such activities are performed so that it can make decisions related to whether the packaged and labeled product conforms to applicable specifications and whether to approve and release the product for distribution.
- **Example 2.** A manufacturer who hires a contractor to perform specific operations within the scope of the manufacturer's responsibilities under the DS CGMP rule is responsible for complying with the requirements related to the contracted operation. For example, a manufacturer who hires a contractor to calibrate its equipment is responsible for complying with the requirements of the DS CGMP rule related to calibrating equipment, even though it is the contractor who is performing that job task.
- **Example 3.** A distributor who contracts with a manufacturer to manufacture a dietary supplement, which the distributor then distributes under its own label, has an obligation to know what and how manufacturing activities are performed so that the distributor can make decisions related to whether the packaged and labeled product conforms to its established specifications and whether to approve and release the product for distribution.

(72 FR 34752 at 34790)

### D. Terms Used in the DS CGMP Rule and In This Document

#### 1. What terms does the DS CGMP rule define?

The DS CGMP rule defines the following terms:

- Actual yield;
- Batch;
- Batch number, lot number, or control number;
- Component;

- Contact surface;
- Ingredient;
- In-process material;
- Lot;
- Microorganisms;
- Pest;
- Physical plant;
- Product complaint;
- Quality;
- Quality control;
- Quality control personnel;
- Representative sample;
- Reprocessing;
- Reserve sample;
- Sanitize;
- Theoretical yield; and
- Water activity.

The DS CGMP rule also explains how we use the following terms:

- Must;
- We; and
- You.

The text of these definitions is available in 21 CFR 111.3.

**2. What definitions from the DS CGMP rule did we copy to this document?**

We copied the definitions of the terms "quality" and "product complaint" (other than the examples in such definition) to this document.

**3. How does the DS CGMP rule define "quality"?**

The DS CGMP rule defines "quality" to mean "that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under sections 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act" [referring to the Federal Food, Drug, and Cosmetic Act] (see 21 CFR 111.3).

**4. How does the DS CGMP rule define "product complaint"?**

The DS CGMP rule defines "product complaint" to mean "any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice (see 21 CFR 111.3).

**5. What does this document mean when it uses the terms "received product" or "product received for packaging or labeling as a dietary supplement"?**

For the purposes of this document, we use the terms "received product" and "product received for packaging or labeling as a dietary supplement" to mean product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier).

**6. What does this document mean when it uses the term "food CGMP"?**

For the purposes of this document, we use the term "food CGMP" to mean the CGMP requirements, in 21 CFR part 110, established for all food.

**7. What does this document mean when it uses the term "required specifications"?**

For the purposes of this document, we use the term "required specifications" to mean specifications that you are required to establish in accordance with 21 CFR 111.70.

**8. What does this document mean when it uses the term "Certificate of Analysis"?**

For the purposes of this document, we use the term "certificate of analysis" to mean a document, provided by the supplier of a component prior to or upon receipt of the component, that documents certain characteristics and attributes of the component.

(72 FR 34752 at 34834)

**9. What does this document mean when it uses the term "scientifically valid method"?**

For the purposes of this document, we use the term "scientifically valid method" to mean a scientific

method that is accurate, precise, and specific for its intended purpose. In other words, we use the term “scientifically valid method” to mean a scientific method that consistently does what it is intended to do. (72 FR 34752 at 34893)

#### E. Other Applicable Statutory Provisions and Regulations

1. **Do other statutory provisions and regulations apply to persons who manufacture, package, label or hold dietary supplements?**

Yes. You must comply with other applicable statutory provisions and regulations under the Federal Food, Drug, and Cosmetic Act related to dietary supplements.

(21 CFR 111.5)

2. **How does the DS CGMP rule relate to the food CGMP rule in 21 CFR part 110?**

In establishing 21 CFR part 111, we:

- Duplicated those requirements in the food CGMP rule (i.e., 21 CFR part 110) that we found to be common to most dietary supplements;
- Did not duplicate those requirements in the food CGMP rule that were not common to most dietary supplements.

3. **What is an example of a requirement in the food CGMP rule that FDA did not duplicate in the DS CGMP rule?**

An example of a requirement in the food CGMP rule that we did not duplicate in the DS CGMP rule is 21 CFR 110.80(b)(4), which requires that food that relies on the control of water activity for preventing the growth of microorganisms be processed to, and maintained at, a safe moisture level. We did not duplicate this requirement because we concluded that it may not be applicable to most dietary supplements. However, to the extent that this requirement is applicable to a particular dietary supplement, a manufacturer would be expected to comply with it.

4. **What should I do if a provision of the DS CGMP rule conflicts with an analogous provision in the food CGMP rule?**

To the extent that the DS CGMP rule conflicts with the food CGMP rule, you would comply with the DS CGMP rule.

(72 FR 34752 at 34764)

#### IV. Written Procedures Required by the DS CGMP Rule

1. **Does the DS CGMP rule require me to establish and follow written procedures?**

Yes. The DS CGMP rule requires you to establish and follow the written procedures shown in Table 3.

**Table 3  
Requirements for Written Procedures**

**Subpart Written Procedures That the DS CGMP rule Requires You to Establish and Follow**

B	Fulfilling the requirements for personnel (21 CFR 111.8)
C	Cleaning the physical plant and pest control (21 CFR 111.16)
D	Fulfilling the requirements for equipment and utensils, including calibrating instruments and controls you use in manufacturing or testing a component or dietary supplement; calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and maintaining, cleaning, and sanitizing, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or dietary supplements (21 CFR 111.25)
F	The responsibilities of quality control personnel, including written procedures for conducting a material review and making a disposition decision, and for approving or rejecting any reprocessing (21 CFR 111.103)
G	Fulfilling the requirements for components, packaging, and labels and for product that you receive for packaging or labeling as a dietary supplement (21 CFR 111.153)
J	Laboratory operations, including written procedures for the tests and examinations you conduct to determine whether specifications are met (21 CFR 111.303)
K	Manufacturing operations (21 CFR 111.353)
L	Packaging and labeling operations (21 CFR 111.403)
M	Holding and distributing operations (21 CFR 111.453)
N	Fulfilling the requirements for returned dietary supplements (21 CFR 111.503)
O	Fulfilling the requirements for product complaints (21 CFR 111.553)

2. **Does the DS CGMP rule require me to establish and follow written procedures for product recalls?**

No. However, we encourage you to refer to our “Guidance for Industry: Product Recalls, Including Removals and Corrections” (Ref. 1) (72 FR 34752 at 34774).

## V. Records Required by the DS CGMP Rule

### 1. What records does the DS CGMP rule require me to make and keep?

The DS CGMP rule requires you to make and keep the records shown in Table 4.

**Table 4**

#### **Records the DS CGMP rule Requires You to Make and Keep**

##### **Subpart Required Records**

- B
  - Written procedures (21 CFR 111.14(b)(1))
  - Documentation of training, including the date of the training, the type of training, and the person(s) trained (21 CFR 111.14(b)(2))
- C
  - Written procedures (21 CFR 111.23(b))
  - Records that show that water, when used in a manner such that the water may become a component of the dietary supplement, meets the requirements of 21 CFR 111.15(e)(2) of the DS CGMP rule (21 CFR 111.23(c))
- D
  - Written procedures (21 CFR 111.35(b)(1))
  - Documentation, either in individual equipment logs or in the batch record (see § 111.260(c) for batch record requirements), of the date of the use, maintenance, cleaning, and sanitizing of equipment, unless such documentation is kept with the batch record (see § 111.260(c) for batch record requirements) (21 CFR 111.35(b)(2))
  - Documentation of any calibration, each time the calibration is performed, for instruments and controls that you use in manufacturing or testing a component or dietary supplement (21 CFR 111.35(b)(3)). The DS CGMP rule establishes specific requirements for what must be in this documentation. You should refer to 21 CFR 111.35(b)(3) for the complete requirements.
  - Written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment (21 CFR 111.35(b)(4))
  - Backup file(s) of current software programs (and of outdated software that is necessary to retrieve records that you are required to keep in accordance with subpart P, when current software is not able to retrieve such records) and of data entered into computer systems that you use to manufacture, package, label, or hold dietary supplements (21 CFR 111.35(b)(5)). The DS CGMP rule establishes specific requirements for these backup files. You should refer to 21 CFR 111.35(b)(5) for the complete requirements.
  - Documentation of the controls that you use to ensure that equipment functions in accordance with its intended use (21 CFR 111.35(b)(6))
- E
  - Documentation of the specifications established (21 CFR 111.95(b)(1))
  - Documentation of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis (21 CFR 111.95(b)(2))
  - Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the dietary supplement meets the specifications for identity, purity, strength, and composition; and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement (21 CFR 111.95(b)(3))
  - Documentation for why the results of appropriate tests or examinations for the product specifications that you selected for testing ensure that the dietary supplement meets all product specifications (21 CFR 111.95(b)(4))
  - Documentation for why any component and in-process testing, examination, or monitoring, and any other information, will ensure that a product specification that is exempted under 21 CFR 111.75(d) is met without verification through periodic testing of the finished batch, including documentation that the selected specifications tested or examined under 21 CFR 111.75 (c)(1) are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage (21 CFR 111.95(b)(5))
  - If you submit a petition to FDA under 21 CFR 111.75(a)(ii), documentation, under the identity testing interim final rule, of FDA's response to a petition submitted under 21 CFR 111.75(a)(1)(ii) providing for an exemption from the provisions of 21 CFR 111.75(a)(1)(i)
- F
  - Written procedures (21 CFR 111.140(b)(1))
  - Written documentation, at the time of performance, that quality control personnel performed the review, approval, or rejection requirements by recording the date that the review, approval, or rejection was performed and the signature of the person performing the review, approval, or

- rejection (21 CFR 111.140(b)(2))
- Documentation of any material review and disposition decision and follow-up (21 CFR 111.140(b)(3)). The DS CGMP rule establishes specific requirements for this documentation. You should refer to 21 CFR 111.140(b)(3) for the complete requirements.
- G
  - Written procedures (21 CFR 111.180(b)(1))
  - Receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels and for products that you receive for packaging or labeling as a dietary supplement (21 CFR 111.180(b)(2))
  - Documentation, at time of performance, that the requirements for components, packaging, labels, and product that is received for packaging or labeling as a dietary supplement were performed (21 CFR 111.180(b)(3)). The DS CGMP rule establishes specific requirements for this documentation. You should refer to 21 CFR 111.180(b)(3) for the complete requirements.
- H The master manufacturing record (21 CFR 111.210). The DS CGMP rule establishes specific requirements for this documentation. You should refer to 21 CFR 111.210 for the complete requirements.
- I The batch production record (21 CFR 111.260). The DS CGMP rule establishes specific requirements for this documentation. You should refer to 21 CFR 111.260 for the complete requirements.
- J
  - Written procedures (21 CFR 111.325(b)(1))
  - Documentation, at time of performance, that laboratory methodology is followed, and the results of testing and examination (21 CFR 111.325(b)(2))
- K Written procedures (21 CFR 111.375(b))
- L Written procedures (21 CFR 111.430(b))
- M
  - Written procedures (21 CFR 111.475(b)(1))
  - Records of product distribution (21 CFR 111.475(b)(2))
- N
  - Written procedures (21 CFR 111.535(b)(1))
  - Any material review and disposition decision on a returned dietary supplement (21 CFR 111.535(b)(2))
  - The results of any testing or examination conducted on a returned dietary supplement to determine compliance with product specifications (21 CFR 111.535(b)(3))
  - Documentation of the reevaluation by quality control personnel of any dietary supplement that is reprocessed and the determination by quality control personnel of whether the reprocessed dietary supplement meets product specifications (21 CFR 111.535(b)(4))
- O
  - Written procedures (21 CFR 111.570(b)(1))
  - A written record of every product complaint that is related to good manufacturing practice (21 CFR 111.570(b)(2)). The DS CGMP rule establishes specific requirements for this documentation. You should refer to 21 CFR 111.570 for the complete requirements.

## VI. Subpart B - Personnel

1. **What does the DS CGMP rule require me to do to prevent microbial contamination from sick or infected personnel?**  
 The DS CGMP rule requires you to take measures to exclude from any operations any person who might be a source of microbial contamination of any material used in the manufacture, packaging, labeling, or holding of a dietary supplement, and establishes several specific measures for you to take.  
 (21 CFR 111.10(a))
2. **What factors should I consider when determining whether a sick or infected employee may be permitted to work?**  
 In addition to the obvious potential sources of microbial contamination, you should consider possibilities for indirect contamination (e.g., whether contamination could spread to areas through common air handling units or ducts).  
 (72 FR 34752 at 34808)
3. **What does the DS CGMP rule require regarding hygienic practices?**  
 The DS CGMP rule requires employees who work in an operation during which adulteration of the component, dietary supplement, or a contact surface could occur must use hygienic practices to the extent necessary to protect against such contamination of components, dietary supplements, or contact surfaces.  
 (21 CFR 111.10(b))
4. **What hygienic practices does the DS CGMP rule identify for me to use to protect against contamination**

### **of components, dietary supplements, or contact surfaces?**

Below, we list the specific hygienic practices identified in the DS CGMP rule. You should refer to 21 CFR 111.10(b) for the complete description associated with each of the items in the list.

- Wearing outer garments;
- Maintaining adequate personal cleanliness;
- Washing and sanitizing hands;
- Removing unsecured jewelry (and other unsecured objects);
- Using gloves made of an impermeable material and maintaining them in an intact, clean and sanitary condition;
- Wearing effective hair restraints;
- Not storing clothing or other personal belongings in areas where components, dietary supplements, or any contact surfaces are exposed or where contact surfaces are washed;
- Not eating food, chewing gum, drinking beverages, or using tobacco products in areas where components, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed; and
- Taking any other precautions necessary to protect against the contamination of components, dietary supplements, or contact surfaces with microorganisms, filth, or any other extraneous materials.

### **5. What does the DS CGMP rule require regarding personnel?**

The DS CGMP rule requires that:

- You have qualified employees who manufacture, package, label, or hold dietary supplements (21 CFR 111.12(a));
- You identify who is responsible for your quality control operations. Each person who is identified to perform quality control operations must be qualified to do so and such responsibilities must be distinct and separate from other responsibilities (21 CFR 111.12(b)); and
- Each person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, to have the education, training, or experience to perform the person's assigned functions (21 CFR 111.12(c)).

### **6. What does the DS CGMP rule require regarding supervisors?**

The DS CGMP rule requires that:

- You assign qualified personnel to supervise the manufacturing, packaging, labeling, or holding of dietary supplements (21 CFR 111.13(a)); and
- Each supervisor whom you use to be qualified by education, training, or experience to supervise (21 CFR 111.13(b)).

### **7. May individuals who I identify to perform quality control operations also perform other functions, such as production functions?**

Yes. However, the DS CGMP rule requires that each person who is identified to perform quality control operations have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations (21 CFR 111.12(b)).

We recommend that, whenever practical, the person performing a given quality control operation be a different person than the person who performed the operation subject to quality control oversight (72 FR 34752 at 34867).

## **VII. Subpart C - Physical Plant And Grounds**

### **1. What does the DS CGMP rule require regarding the physical plant and grounds?**

The DS CGMP rule:

- Requires you to keep the grounds of your physical plant in a condition that protects against the contamination of components, dietary supplements, or contact surfaces, and establishes several specific measures for you to take to do this (21 CFR 111.15(a));
- Requires you to maintain your physical plant in a clean and sanitary condition, and in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated (21 CFR 111.15(b)); and
- Establishes specific requirements for:
  - Cleaning compounds, sanitizing agents, pesticides, and other toxic materials (21 CFR 111.15(c));
  - Pest control (21 CFR 111.15(d));
  - Plumbing and sewage (21 CFR 111.15(f) and (g));
  - Bathrooms and hand washing facilities (21 CFR 111.15(h) and (i));

- Trash disposal (21 CFR 111.15(j));
- Sanitation supervisors (21 CFR 111.15)(k));
- The design and construction of the physical plant (21 CFR 111.20); and
- The water supply (see 21 CFR 111.15(e) and Questions 2 through 7 in section VIII of this document).

**2. What does the DS CGMP rule require regarding the water supply when the water does not become a component of a dietary supplement?**

The DS CGMP rule requires you to provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement.

(21 CFR 111.15(e)(1))

**3. What is an example of water that does not become a component of the dietary supplement?**

Water used to wash floors does not become a component of a dietary supplement.

(72 FR 34752 at 34816)

**4. What does the DS CGMP rule require regarding the water supply when the water may become a component of a dietary supplement?**

The DS CGMP rule requires that, at a minimum, water used in a manner such that the water may become a component of the dietary supplement comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement.

(21 CFR 111.15(e)(2))

**5. What are examples of water that may become a component of a dietary supplement?**

Examples of water that may become a component of a dietary supplement include water that contacts components, dietary supplements, or any contact surface.

(72 FR 34752 at 34816)

**6. What steps should I take if I use a municipal water supply?**

If you use a municipal water supply, you should take steps to ensure that you are at all times aware of problems, such as an acute problem with microbial contamination or a long-term problem associated with lead pipes present in some parts of the city water supply, that may not be reflected in the municipal water report.

(72 FR 34752 at 34821)

**7. What does the CGMP rule require regarding water from a private source, such as a well, used in a manner such that the water may become a component of the dietary supplement?**

The DS CGMP rule requires that water from a private source, used in a manner such that the water may become a component of the dietary supplement, comply with any State and local requirements and not contaminate the dietary supplement. Satisfying this requirement may involve performing appropriate water treatment procedures including filtration, sedimentation, and chlorination).

(21 CFR 111.15(e)(2); 72 FR 34752 at 34817)

## **VIII. Subpart D - Equipment And Utensils**

**1. What kinds of equipment and utensils are covered by the DS CGMP rule?**

Equipment and utensils used in manufacturing, packaging, labeling or holding operations that are covered by the DS CGMP rule include:

- Equipment used to hold or convey;
- Equipment used to measure;
- Equipment using compressed air or gas;
- Equipment used to carry out processes in closed pipes and vessels; and
- Equipment used in automated, mechanical, or electronic systems

(21 CFR 111.27(a)(1))

**2. What requirements does the DS CGMP rule establish regarding equipment and utensils?**

The DS CGMP rule establishes requirements for:

- The design, construction, installation, use and maintenance of equipment and utensils, including specific requirements for the seams of equipment and utensils, cold storage compartments, instruments or controls used to measure or record, and compressed air or other gases (21 CFR 111.27(a)); and
- Calibrating equipment and controls (21 CFR 111.27(b)).

**3. What does the DS CGMP rule require regarding automated, mechanical, or electronic equipment that**

## **you use to manufacture, package, label or hold a dietary supplement?**

For any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, the DS CGMP rule requires you to:

- Design or select equipment to ensure that dietary supplement specifications are consistently met (21 CFR 111.30(a));
- Determine the suitability of the equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process (21 CFR 111.30(b));
- Routinely calibrate, inspect, or check the equipment to ensure proper performance. Your quality control personnel must periodically review these calibrations, inspections, or checks (21 CFR 111.30(c));
- Establish and use appropriate controls for automated, mechanical, and electronic equipment (including software for a computer controlled process) to ensure that any changes to the manufacturing, packaging labeling, holding, or other operations are approved by quality control personnel and instituted only by authorized personnel (21 CFR 111.30(d)); and
- Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by quality control personnel (21 CFR 111.30(e)).

## **IX. Subpart E - Requirement To Establish A Production And Process Control System**

### **A. General Requirements of Subpart E**

#### **1. What does Subpart E of the DS CGMP rule require regarding the design and implementation of a production and process control system?**

Subpart E of the DS CGMP rule requires you to design (21 CFR 111.60(a)) and implement (21 CFR 111.55) a system of production and process controls covering all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and to ensure that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

#### **2. Does the DS CGMP rule require quality control personnel to review and approve all aspects of the production and process control system?**

Yes.

(21 CFR 111.60(b))

#### **3. What does Subpart E of the DS CGMP rule require regarding quality control operations?**

Subpart E of the DS CGMP rule requires you to implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(21 CFR 111.65)

### **B. Requirements to Establish Specifications**

#### **1. What specifications does the DS CGMP rule require me to establish?**

The DS CGMP rule requires you to establish:

- A specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.70(a));
- Specifications for components you use in the manufacture of a dietary supplement (21 CFR 111.70(b));
- Specifications for the in-process production (21 CFR 111.70(c));
- Specifications for dietary supplement labels and packaging (21 CFR 111.70(d));
- Product specifications for the finished batch of the dietary supplement (21 CFR 111.70(e));
- Specifications for product you receive from a supplier for packaging or labeling as a dietary supplement (21 CFR 111.70(f)); and
- Specifications for the packaging and labeling of the finished packaged and labeled dietary supplements (21 CFR 111.70g)).

#### **2. Does the DS CGMP rule require me to establish specifications for parameters such as dissolution, disintegration, and bioavailability?**

No.

(72 FR 34752 at 34851)

#### **3. Does the DS CGMP rule require me to establish an "expiration date" (or a "shelf date" or "best if**

**used by” date)?**

No.

(72 FR 34752 at 34855)

### **C. Requirements to Determine Whether Specifications Are Met**

#### **1. Does the DS CGMP rule require me to determine whether required specifications are met?**

Yes. The DS CGMP rule requires you to determine whether each of the following required specifications are met:

- Specifications for components (21 CFR 111.75(a));
- Specifications for the in-process production (21 CFR 111.75(b));
- Specifications for the finished batch of the dietary supplement (21 CFR 111.75(c) and (d));
- Specifications for product you receive from a supplier for packaging or labeling as a dietary supplement (21 CFR 111.75(e));
- Specifications for dietary supplement labels and packaging (21 CFR 111.75(f)); and
- Specifications for the packaging and labeling of the finished packaged and labeled dietary supplements (21 CFR 111.75(g)).

#### **2. Should I have data to support any specifications I establish for parameters such as dissolution, disintegration, and bioavailability?**

Yes. Although the DS CGMP rule does not require you to establish specifications for parameters such as dissolution, disintegration, and bioavailability, if you establish such specifications you should have data to support that such specifications are met.

(72 FR 34752 at 34851)

#### **3. Should I have data to support any expiration date (or “shelf date” or “best if used by” date) that will place on a product label?**

Yes. Although the DS CGMP rule does not require you to establish an “expiration date” (or a “shelf date” or “best if used by” date), you should have data to support any such date that you place on a product label

(72 FR 34752 at 34855)

#### **4. What does the DS CGMP rule require regarding the tests and examinations I use to determine whether specifications are met?**

The DS CGMP rule requires that:

- You ensure that the tests and examinations you use to determine whether the specifications are met are appropriate, scientifically valid methods (21 CFR 111.75(h)(1)); and
- The tests and examinations you use include at least one of the following (21 CFR 111.75(h)(2)):
  - Gross organoleptic analysis (21 CFR 111.75(h)(2)(i));
  - Macroscopic analysis (21 CFR 111.75(h)(2)(ii));
  - Microscopic analysis (21 CFR 111.75(h)(2)(iii));
  - Chemical analysis (21 CFR 111.75(h)(2)(iv)); or
  - Other scientifically valid methods (21 CFR 111.75(h)(2)(v)).

#### **5. Does the DS CGMP rule require any verification that a finished batch of dietary supplement meets product specifications?**

Yes. The DS CGMP rule requires you to verify that a subset of finished dietary supplement batches (which you identify through a sound statistical sampling plan) meets product specifications (i.e., specifications that the DS CGMP rule requires you to establish under 21 CFR 111.70(e)), unless you choose to verify that the product specifications are met for every finished batch (21 CFR 111.75(c)). To do so, the DS CGMP rule requires that:

- You select one or more established specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if determined to be in compliance with specifications by testing or examination of the finished batch of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (with the exception of those product specifications that are exempted from this requirement) (21 CFR 111.75(c)(1) and 21 CFR 111.75(d));
- You conduct appropriate tests or examinations to determine compliance with these specifications (21 CFR 111.75(c)(2));
- You provide adequate documentation of your basis for determining that compliance with the selected specification(s), through the use of appropriate tests or examinations, will ensure that your finished

batch of the dietary supplement meets all product specifications established under 21 CFR 111.70(e) (21 CFR 111.75(c)(3)); and

- Your quality control personnel review and approve this documentation (21 CFR 111.75(c)(4)).

**6. Is there any exemption from the requirement of the DS CGMP rule regarding verification that a finished batch of dietary supplement meets product specifications?**

Yes (21 CFR 111.75(d)). We realize that there may well be some specifications that you may not be able to test for at the finished batch stage. For example, you may determine that you could not verify, by testing for compliance with the specifications for identity and composition, that the purity specification is met, and there may be no scientifically valid method for testing or examining the finished batch to evaluate the purity in the finished batch of dietary supplement. In such a case, the DS CGMP rule provide that you can document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that this product specification is met without verification through periodic testing of the finished batch, provided your quality control personnel review and approve that documentation (21 CFR 111.75(d)). For example, you could exempt the specification for purity from the requirement in 21 CFR 111.75(c)(1) through, for example, documentation that meeting component and specifications for strength is sufficient, or through documentation that in-process monitoring is sufficient, provided your quality control personnel review and approve such documentation (21 CFR 111.75(d)).

(72 FR 34752 at 34850)

**7. Does the DS CGMP rule require me to establish a corrective action plan for use when an established specification is not met?**

Yes.

(21 CFR 111.75(i))

**8. What are the consequences of not meeting a specification that I must establish under 21 CFR 111.70?**

The consequences of not meeting a specification that the DS CGMP rule requires you to establish under 21 CFR 111.70 depend on which specification is not met (21 CFR 111.77). Table 5 shows these consequences.

**Table 5  
Consequences of Not Meeting an Established Specification**

<b>Specification Provision</b>	<b>Description of Specification</b>	<b>Consequence of Not Meeting the Established Specification</b>
21 CFR 111.70(a)	Any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record	Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))
21 CFR 111.70(b)(1)	Identity of a Component	Reject the component and not use it in the manufacture of a dietary supplement (21 CFR 111.77(b))
21 CFR 111.70(b)(2)	Component specifications necessary to ensure that specifications for the purity, strength and composition of the dietary supplement are met	Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))
21 CFR 111.70(b)(3)	Limits on contaminants	Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))
21 CFR 111.70(c)	In-process production	Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))
21 CFR 111.70(d)	Dietary supplement labels and packaging	Reject the finished batch of the dietary supplement and not package or label the

21 CFR 111.70(e)	Product specifications	dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a)) Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))
21 CFR 111.70(f)	Product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)	Reject the product and not package or label it for distribution as a dietary supplement (21 CFR 111.77(c))
21 CFR 111.70(g)	Packaging and labeling of the finished batch of the dietary supplement	Reject the finished batch of the dietary supplement and not package or label the dietary supplement for distribution unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing (21 CFR 111.77(a))

**9. What does the DS CGMP rule require regarding treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when a specification is not met?**

The DS CGMP rule requires that:

- You not reprocess a rejected dietary supplement, or treat or provide an in-process adjustment to a component, packaging, or label to make it suitable for use in the manufacture of a dietary supplement unless quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment (21 CFR 111.90(a));
- You not reprocess any dietary supplement, or treat or provide an in-process adjustment to a component to make it suitable for use in the manufacture of a dietary supplement, unless quality control personnel conduct a material review and make a disposition decision based on a scientifically valid reason and approves the reprocessing, treatment, or in-process adjustment (21 CFR 111.90(b)); and
- Any batch of dietary supplement that is reprocessed (or that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the dietary supplement) must meet requirements in 21 CFR 111.123(b) and be approved by quality control personnel before releasing for distribution (21 CFR 111.90(c)).

**D. Specific Requirements Regarding Specifications for Dietary Ingredients and Other Components**

**1. What does the DS CGMP rule require me to do to verify the identity of each dietary ingredient that I use in the manufacture of a dietary supplement?**

The DS CGMP rule requires you to conduct at least one appropriate test or examination to verify the identity of any dietary ingredient, unless you petition us to exempt you from this requirement and we approve your petition (21 CFR 111.75(a)(1)). It is up to you to determine the appropriate test(s) or examination(s) necessary to verify the identity of a dietary ingredient. In some cases, a single test or examination may be all that is needed to verify the identity of a dietary ingredient; in other cases, it may be necessary to conduct more than one test or examination (72 FR 34752 at 34847).

**2. Is there an alternative to the requirement of 21 CFR 111.75(a)(1) for me to verify the identity of each dietary ingredient that I use in the manufacture of a dietary supplement?**

Yes. You may petition us for an alternative to the required 100 percent identity testing of components that are dietary ingredients (see 21 CFR 111.75(a)(1)(ii) of the identity testing interim final rule). You would submit the petition as a citizen petition in accordance with the provisions of 21 CFR 10.30 (21 CFR 111.75(a)(1)(ii)).

Your petition must set forth the scientific rationale, and be accompanied by the supporting data and information, for proposed alternative testing that will demonstrate that there is no material diminution of assurance, compared to the assurance provided by 100 percent identity testing, of the identity of the dietary ingredient before use when the dietary ingredient is obtained from one or more suppliers identified in the petition (21 CFR 111.75(a)(1)(ii)).

If FDA grants the petition, you would conduct the tests and examinations for the dietary ingredient, otherwise required under 21 CFR 111.75(a)(1)(i), under the terms specified by FDA when the petition is granted (21 CFR 111.75(a)(1)(ii)).

3. **What does the DS CGMP rule require me to do to ensure that specifications are met for components that I use in the manufacture of a dietary supplement?**

The DS CGMP rule requires you to confirm the identity of components, and determine whether other specifications for components (including dietary ingredients), are met, either by conducting appropriate tests or examinations or by relying on a certificate of analysis from the supplier of the component.

(21 CFR 111.75(a)(2))

4. **What does the CGMP rule require me to do if I rely on a Certificate of Analysis from a supplier to confirm the identity of a component other than a dietary ingredient, or to determine whether any other component specifications are met?**

The DS CGMP rule requires that:

- You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations (21 CFR 111.75(a)(2)(ii)(A)).
- The certificate of analysis include a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations (21 CFR 111.75(a)(2)(ii)(B)).
- You maintain documentation of how you qualified the supplier (21 CFR 111.75(a)(2)(ii)(C)).
- You periodically re-confirm the supplier's certificate of analysis (21 CFR 111.75(a)(2)(ii)(D)).
- Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier (21 CFR 111.75(a)(2)(ii)(E)).

**E. Requirements for Representative and Reserve Samples**

1. **What representative samples does the DS CGMP rule require me to collect?**

The DS CGMP rule requires you to collect representative samples of the following materials:

- Each unique lot of components, packaging, and labels that you use (21 CFR 111.80(a));
- In-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, strength, and composition of dietary supplements (21 CFR 111.80(b));
- A subset of finished batches of each dietary supplement that you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution (21 CFR 111.80(c));
- Each unique shipment, and each unique lot within each unique shipment, of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier (21 CFR 111.80(d)); and
- Each lot of packaged and labeled dietary supplements (21 CFR 111.80(e)).

2. **Why does the DS CGMP rule require me to collect and to hold representative samples?**

The DS CGMP rule requires you to collect representative samples to determine whether applicable specifications are met.

(21 CFR 111.80)

3. **What reserve samples does the DS CGMP rule require me to collect and hold?**

The DS CGMP rule requires you to collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute. This would include dietary supplements that you package and label in bulk.

(21 CFR 111.83(a))

4. **Why does the DS CGMP rule require me to collect and to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to collect and hold reserve samples of packaged and labeled dietary supplements for use in appropriate investigations, such as consumer complaint investigations.

(21 CFR 111.83(b)(3) and 21 CFR 111.465(b))

5. **How many reserve samples does the DS CGMP rule require me to collect and hold?**

The DS CGMP rule requires that the amount of reserve samples you collect and hold consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications.

(21 CFR 111.83(b)(4))

6. **How does the DS CGMP rule require me to identify reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to identify reserve samples with the batch, lot, or control number.  
(21 CFR 111.83(b)(2))

**7. What container-closure system does the DS CGMP rule require me to use to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to use the following container-closure systems to hold reserve samples of dietary supplements:

- If you are distributing a packaged and labeled dietary supplement, the DS CGMP rule requires you to keep the reserve samples in a container-closure system that is the same as the container-closure system in which the dietary supplement is distributed.
- If you are distributing a dietary supplement for packaging and labeling, the DS CGMP rule requires you to keep the reserve samples in a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which you distributed the dietary supplement for packaging and labeling elsewhere. For example, if you distribute product in bulk using a polyethylene bottle that can hold 50 kilograms of the product, and there is an air space above the product, you would hold the reserve samples in a polyethylene bottle with an air space. However, you would use a bottle sized to fit the smaller amount you are holding in reserve.

(21 CFR 111.83(b)(1); 72 FR 34752 at 34904)

**8. How long does the DS CGMP rule require me to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to hold reserve samples of packaged and labeled dietary supplements for:

- One year past the shelf life date (if shelf life dating is used); or
- Two years from the date of distribution of the last batch of dietary supplements associated with the reserve sample.

(21 CFR 111.83(b)(3); 72 FR 34752 at 34905)

**X. Subpart F – Production and Process Control: Requirements For Quality Control**

**1. What does the DS CGMP rule require quality control personnel to do?**

The DS CGMP rule requires quality control personnel to ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(21 CFR 111.105)

**2. What operations does the DS CGMP rule require quality control personnel to perform?**

The DS CGMP rule requires quality control personnel to perform operations that include:

- Approving or rejecting all processes, specifications, written procedures, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, strength, or composition of a dietary supplement (21 CFR 111.105(a));
- Reviewing and approving the documentation setting forth the basis for qualification of any supplier (21 CFR 111.105(b));
- Reviewing and approving the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that the identity, purity, strength, and composition of the dietary supplement are met (21 CFR 111.105(c));
- Reviewing and approving the documentation setting forth the basis for why the results of appropriate tests or examinations for each product specification selected under 21 CFR 111.75(c)(1) will ensure that the finished batch of the dietary supplement meets product specifications (21 CFR 111.105(d));
- Reviewing and approving the basis and the documentation for why any product specification is exempted from the verification requirements in 21 CFR 111.75(c)(1), and for 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 (21 CFR 111.105(e));
- Ensuring that all representative samples are collected (21 CFR 111.105(f));
- Ensuring that all reserve samples are collected and held (21 CFR 111.105(g));
- Determining whether all specifications established under 21 CFR 111.70(a) are met (21 CFR 111.105(h));
- Laboratory operations (21 CFR 111.110);
- Operations regarding material review and disposition decisions (21 CFR 111.113);
- Operations regarding equipment, instruments, and controls (21 CFR 111.117);
- Operations regarding components, packaging, and labels before use in the manufacture of a dietary

supplement (21 CFR 111.120);

- Operations regarding the master manufacturing record, the batch production record, and manufacturing operations (21 CFR 111.123);
- Packaging and labeling operations (21 CFR 111.127);
- Operations regarding returned dietary supplements (21 CFR 111.130); and
- Operations regarding product complaints (21 CFR 111.135).

**3. Who conducts a material review and disposition decision?**

Quality control personnel conduct all required material reviews and make all required disposition decisions (21 CFR 111.87). However, qualified individuals who are not assigned as quality control personnel may participate in the material review, e.g., by providing relevant information or analysis (72 FR 34752 at 34865).

**4. When does the DS CGMP rule require quality control personnel to do to conduct a material review and disposition decision?**

The DS CGMP rule identifies five circumstances when quality control personnel must conduct a material review and make a disposition decision (21 CFR 111.113(a)):

- A specification established in accordance with 21 CFR 111.70 is not met (21 CFR 111.113(a)(1));
- A batch deviates from the master manufacturing record, including when any step established in the master manufacturing record is not completed and including any deviation from specifications (21 CFR 111.113(a)(2));
- There is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record (21 CFR 111.113(a)(3));
- Calibration of an instrument or control suggests a problem that may have resulted in a failure to ensure the quality of a batch or batches of a dietary supplement (21 CFR 111.113(a)(4)); or
- A dietary supplement is returned (21 CFR 111.113(a)(5)).

**5. When does the DS CGMP rule require quality control personnel to reject a component, dietary supplement, packaging or label?**

The DS CGMP rule requires quality control personnel to reject a component, dietary supplement, packaging, or label when:

- There is a deviation or unanticipated occurrence during the production and in-process control system that results in or could lead to adulteration of a component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record (unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence) (21 CFR 111.113(b)(1)).
- When a specification that you are required to establish is not met (unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in 21 CFR 111.77) (21 CFR 111.113(b)(2)).

**6. When does the DS CGMP rule require documentation of a material review and disposition decision?**

The DS CGMP rule requires the person who conducts a material review and makes the disposition decision to document the material review and disposition decision at the time of performance.

(21 CFR 111.113(c))

**XI. Subpart G – Production and Process Control System; Requirements For Components, Packaging, And Label And For Product That Is Received For Packaging Or Labeling As A Dietary Supplement**

**A. Requirements for Components**

**1. What visual examinations does the DS CGMP rule require me to conduct for components of dietary supplements?**

The DS CGMP rule requires you to visually examine the supplier's invoice, guarantee, or certification, and each immediate container or grouping of immediate containers, in a shipment of components.

(21 CFR 111.155(a) and (b))

**2. How long does the DS CGMP rule require me to quarantine components?**

The DS CGMP rule requires you to quarantine components until:

- You collect representative samples (21 CFR 111.155(c)(1));
- Quality control personnel review and approve the results of any tests or examinations conducted on the representative samples (21 CFR 111.155(c)(2));
- Quality control personnel approve the components for use in the manufacture of a dietary supplement (21 CFR 111.155(c)(3)); and

- Quality control personnel release the components from quarantine (21 CFR 111.155(c)(3)).
3. **Does the DS CGMP rule require me to assign a unique identifier to components?**

Yes. The DS CGMP rule requires you to identify each unique lot within each unique shipment of components you receive (and any lot of components you produce) in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g. quarantined, approved, or rejected), and to the dietary supplement that you manufactured and distributed.

(21 CFR 111.155(d)(1))
  4. **When does the DS CGMP rule require me to use the unique identifier that I assign to components?**

The DS CGMP rule requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components you receive and any lot of components you produce.

(21 CFR 111.155(d)(2))
  5. **How does the DS CGMP rule require me to hold components?**

The DS CGMP rule requires you to hold components under conditions that will protect against contamination and deterioration, and avoid mix-ups.

(21 CFR 111.155(e))
  6. **What does the DS CGMP rule require to be included in a Certificate of Analysis that accompanies a component?**

The DS CGMP rule requires a certificate of analysis to include:

    - A description of the test or examination method(s) used;
    - Limits of the test or examinations; and
    - Actual results of the tests or examinations.

(21 CFR 111.75(a)(2)(ii)(B))
  7. **Does the DS CGMP rule establish any requirements specific to animal-derived ingredients?**

No. However, you are responsible to comply with any other regulations applying to foods containing animal-derived ingredients. For example, if you manufacture a dietary supplement containing cattle-derived material, you would be responsible to comply with the requirements for cattle-derived material established in 21 CFR 189.5. As another example, if you manufacture a dietary supplement containing ingredients derived from fish, you would be responsible to comply with applicable requirements for fish and fishery products in 21 CFR part 123.

(72 FR 34752 at 34838)

## B. Requirements for Packaging and Labels

1. **What visual examinations does the DS CGMP rule require me to conduct for packaging and labels?**

The DS CGMP rule requires you to visually examine the supplier's invoice, guarantee, or certification, and each immediate container or grouping of immediate containers, in a shipment.

(21 CFR 111.160(a) and (b))
2. **How long does the DS CGMP rule require me to quarantine packaging and labels?**

The DS CGMP rule requires you to quarantine packaging and labels until:

  - You collect representative samples and, at a minimum, conduct a visual identification of the immediate containers and closures (21 CFR 111.160(c)(1));
  - Quality control personnel review and approve the results of any tests or examinations conducted on the packaging and labels (21 CFR 111.160(c)(2));
  - Quality control personnel approve the packaging and labels for use in the manufacture of a dietary supplement (21 CFR 111.160(c)(3)); and
  - Quality control personnel release the packaging and labels from quarantine (21 CFR 111.160(c)(3)).
3. **Does the DS CGMP rule require me to assign a unique identifier to packaging and labels?**

Yes. The DS CGMP rule requires you to identify each unique lot within each unique shipment of packaging and labels in a manner that allows you to trace the lot to the supplier, the date received, the name of the packaging and label, the status of the packaging and label (e.g., quarantined, approved, or rejected), and to the dietary supplement that you distributed.

(21 CFR 111.160(d)(1))
4. **When does the DS CGMP rule require me to use the unique identifier that I assign to packaging and labels?**

The DS CGMP rule requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of packaging and labels.

(21 CFR 111.160(d)(2))

**5. How does the DS CGMP rule require me to hold packaging and labels?**

The DS CGMP rule requires you to hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mix-ups.

(21 CFR 111.160(e))

**C. Requirements for Received Product**

**1. What visual examinations does the DS CGMP rule require me to conduct for received product (i.e. product that I receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier))?**

The DS CGMP rule requires you to visually examine the supplier's invoice, guarantee, or certification, and each immediate container or grouping of immediate containers, in a shipment.

(21 CFR 111.165(a) and (b))

**2. How long does the DS CGMP rule require me to quarantine received product?**

The DS CGMP rule requires you to quarantine received product until:

- You collect representative samples (21 CFR 111.165 (c)(1));
- Quality control personnel review and approve the documentation to determine whether the received product meets specifications (21 CFR 111.165(c)(2));
- Quality control personnel approve the received product for packaging or labeling as a dietary supplement (21 CFR 111.165(c)(3)); and
- Quality control personnel release the received product from quarantine (21 CFR 111.165(c)(3)).

**3. Does the DS CGMP rule require me to assign a unique identifier to received product?**

Yes. The DS CGMP rule requires you to identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product you packaged or labeled and distributed as a dietary supplement.

(21 CFR 111.165(d)(1))

**4. When does the DS CGMP rule require me to use the unique identifier that I assign to received product?**

The DS CGMP rule requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product.

(21 CFR 111.165(d)(2))

**5. How does the DS CGMP rule require me to hold received product?**

The DS CGMP rule requires you to hold received product under conditions that will protect against contamination and deterioration, and avoid mix-ups.

(21 CFR 111.165(e))

**D. Requirements for Rejected Components, Packaging, Labels and Received Product**

**1. What does the DS CGMP rule require me to do with rejected components, packaging, and labels, and with rejected products received for packaging or labeling as a dietary supplement?**

The DS CGMP rule requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product you receive for packaging or labeling as a dietary supplement, that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

(21 CFR 111.170)

**XII. Subpart H – Production and Process Control System: Requirements for a Master Manufacturing Record**

**1. Does the DS CGMP rule require me to establish a master manufacturing record?**

Yes. The DS CGMP rule requires you to prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch (21 CFR 111.205(a)). The master manufacturing record must establish controls and procedures to ensure that each batch of dietary supplement you manufacture meets those specifications (21 CFR 111.205(b)(2)).

**2. What specifications does the DS CGMP rule require the master manufacturing record to identify?**

The DS CGMP rule requires the master manufacturing record to identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(21 CFR 111.205(b))

### 3. **What does the DS CGMP rule require the master manufacturing record to include?**

The DS CGMP rule requires the master manufacturing record to include:

- The name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size (21 CFR 111.210(a));
- A complete list of components to be used (21 CFR 111.210(b));
- An accurate statement of the weight or measure of each component to be used (21 CFR 111.210(c));
- The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement (21 CFR 111.210(d));
- A statement of any intentional overage amount of a dietary ingredient (21 CFR 111.210(e)) (the amount of overage should be limited to the amount needed to meet the weight or measure of each dietary ingredient that will be declared on the Supplement Facts label of the dietary supplement) (72 FR 34752 at 34884);
- A statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made (21 CFR 111.210(f));
- A description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label (21 CFR 111.210(g)); and
- Written instructions, including the following:
  - Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.210(h)(1));
  - Procedures for sampling and a cross-reference to procedures for tests or examinations (21 CFR 111.210(h)(2));
  - Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.210(h)(3));
    - Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component (21 CFR 111.210(h)(3)(i)); and
    - For manual operations, such specific actions must include one person weighing or measuring a component and another person verifying the weight or measure, and one person adding the component and another person verifying the addition (21 CFR 111.210(h)(3)(ii));
  - Special notations and precautions to be followed (21 CFR 111.210(h)(4)); and
  - Corrective action plans for use when a specification is not met (21 CFR 111.210(h)(5)).

## **XIII. Subpart I – Production and Process Control System: Requirements for a Batch Production Record**

### 1. **Does the DS CGMP rule require me to establish a batch production record?**

Yes. The DS CGMP rule requires you to prepare a batch production record every time you manufacture a batch of a dietary supplement.

(21 CFR 111.255(a))

### 2. **What does the DS CGMP rule require regarding the batch production record?**

The DS CGMP rule requires that:

- Your batch production record accurately follow the appropriate master manufacturing record; and
- You perform each step in the production of the batch.

(21 CFR 111.255(c))

### 3. **What does the DS CGMP rule require the batch production record to include?**

The DS CGMP rule requires the batch production record to include complete information relating to the production and control of each batch (21 CFR 111.255(b)). Specifically, the DS CGMP rule requires the batch production record to include:

- The batch, lot, or control number of the finished batch of dietary supplement, each lot of packaged and labeled dietary supplement from the finished batch of dietary supplement, and each lot of dietary supplement, from the finished batch of dietary supplement, that you distribute to another person for packaging or labeling (21 CFR 111.260(a));
- The identity of equipment and processing lines used in producing the batch (21 CFR 111.260(b));
- The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines use in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained (21 CFR 111.260(c));
- The unique identifier you assigned to each component (or, when applicable, to a product that you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used (21 CFR 111.260(d));
- The identity and weight or measure of each component used (21 CFR 111.260(e));
- A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing (21 CFR 111.260(f));
- The actual results obtained during any monitoring operation (21 CFR 111.260(g));
- The results of any testing or examination performed during the batch production, or a cross-reference to such results (21 CFR 111.260(h));
- Documentation that the finished dietary supplement meets specifications established in accordance with 21 CFR 111.70(e) and (g) (21 CFR 111.260(i));
- Documentation, at the time of performance, of the manufacture of the batch, including the date on which each step of the master manufacturing record was performed and the initials of the persons performing each step (21 CFR 111.260(j));
- Documentation, at the time of performance, of packaging and labeling operations, including:
  - The unique identifier you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels (21 CFR 111.260(k)(1));
  - An actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record (21 CFR 111.260(k)(2)); and
  - The results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference to the physical location of such results (21 CFR 111.260(k)(1));
- Documentation at the time of performance that quality control personnel reviewed the batch production record, approved or rejected any reprocessing or repackaging, approved and released (or rejected) the batch for distribution, and approved and released (or rejected) the packaged and labeled dietary supplement, including any repackaged or relabeled dietary supplement (21 CFR 111.260(l));
- Documentation at the time of performance of any required material review and disposition decision (21 CFR 111.260(m)); and
- Documentation at the time of performance of any reprocessing (21 CFR 111.260(n)).

#### **XIV. Subpart J – Production and Process Control System: Requirements for Laboratory Operations**

##### **1. What does the DS CGMP rule require regarding facilities to perform testing and examinations?**

The DS CGMP rule requires you to use adequate laboratory facilities to perform testing and examinations. (21 CFR 111.310)

##### **2. What laboratory control processes does the DS CGMP rule require me to establish and follow?**

The DS CGMP rule requires you to establish and follow laboratory control processes that include:

- Use of criteria for establishing appropriate specifications (21 CFR 111.315(a));
- Use of sampling plans for obtaining representative samples (21 CFR 111.315(b));
- Use of criteria for selecting appropriate examination and testing methods (21 CFR 111.315(c));
- Use of criteria for selecting standard reference materials used in performing tests and examinations (21 CFR 111.315(d)); and
- Use of test methods and examinations in accordance with established criteria (21 CFR 111.315(e)).

##### **3. Does the DS CGMP rule require quality control personnel to review and approve the laboratory control processes I establish and follow?**

Yes.

(21 CFR 111.315)

4. **How should I determine which reference materials to use in performing tests and examinations?**

Reference materials should be appropriate to the assay procedure for which they are used. We recommend that you use compendia reference standards whenever possible. If no compendia reference standard exists, we recommend that you establish appropriately characterized in-house materials prepared from representative lots. Such in-house materials should be of the highest purity that can be obtained by reasonable effort and should be thoroughly characterized to ensure their identity, purity, quality, and strength.

(72 FR 34752 at 34892)

5. **What does the DS CGMP rule require me to do regarding laboratory methods I use for testing and examination?**

The DS CGMP rule requires you to:

- Verify that the laboratory examination and testing methodologies are appropriate for their intended use (21 CFR 111.320(a)); and
- Identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met (21 CFR 111.320(b)).

6. **What is an example of a scientifically valid method?**

An example of a scientifically valid method can be one that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research.

(72 FR 34752 at 34893)

7. **Does the DS CGMP rule require me to use a "validated" scientific method to perform tests or examinations?**

No, it requires you to use a scientifically "valid" method. However, we recommend that you use a "validated" scientific method whenever one is available.

(72 FR 34752 at 34893)

8. **What does "validating" a scientific method involve?**

In general, "validating" a scientific method involves evaluating the method on multiple occasions or in multiple test facilities. Official methods are validated in collaborative studies using several laboratories under identical conditions. Other method validations are conducted in a single laboratory by repeating the same test multiple times. Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.

(72 FR 34752 at 34893)

9. **Where can I find validated methods?**

Validated methods can be found in official references, such as AOAC International, United States Pharmacopoeia (USP), and others

(72 FR 34752 at 34893)

10. **What should I do if I modify a validated method?**

If you modify an officially validated method, you should:

- Document the reason for the modification;
- Have data to show that the modified method produces results that are at least as accurate and reliable as the established method for the material being tested; and
- Have complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions you use in your laboratory operations.

(72 FR 34752 at 34894)

## **XV. Subpart K – Production and Process Control System: Requirements for Manufacturing Operations**

1. **How does the DS CGMP rule require me to design or select manufacturing processes?**

The DS CGMP rule requires you to design or select manufacturing processes to ensure that product specifications are consistently met.

(21 CFR 111.355)

2. **How does the DS CGMP rule require me to conduct manufacturing operations?**

The DS CGMP rule requires you to conduct all manufacturing operations in accordance with adequate sanitation principles.

(21 CFR 111.360)

3. **What precautions does the DS CGMP rule require me to take to prevent contamination during manufacturing operations?**

The DS CGMP rule requires you to take all necessary precautions during the manufacture of a dietary supplement to prevent contamination of components or dietary supplements, including the following specific precautions:

- Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination (21 CFR 111.365(a));
- Washing or cleaning components that contain soil or other contaminants (21 CFR 111.365(b));
- Using water that, at a minimum, complies with the applicable Federal, State, and local requirements and does not contaminate the dietary supplement when the water may become a component of the finished batch of dietary supplement (21 CFR 111.365(c));
- Performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components (21 CFR 111.365(d));
- Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (aw), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition (21 CFR 111.365(e));
- Holding components and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and dietary supplements from becoming adulterated (21 CFR 111.365(f));
- Identifying and holding any components or dietary supplements, for which a material review and disposition decision is required, in a manner that protects components or dietary supplements that are not under a material review against contamination and mix-ups with those that are under a material review (21 CFR 111.365(g));
- Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary supplements against contamination (21 CFR 111.365(h));
- Using effective measures to protect against the inclusion of metal or other foreign material in components or dietary supplements (21 CFR 111.365(i));
- Segregating and identifying all containers for a specific batch of dietary supplements to identify their contents and, when necessary, the phase of manufacturing (21 CFR 111.365(j)); and
- Identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing (21 CFR 111.365(k)).

#### 4. **What does the DS CGMP rule require me to do with a rejected dietary supplement?**

The DS CGMP rule requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any dietary supplement that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

(21 CFR 111.370)

## **XVI. Subpart L – Production and Process Control System: Requirements for Packaging and Labeling Operations**

### 1. **What does the DS CGMP rule require me to do regarding packaging and labels?**

The DS CGMP rule requires you to:

- Take necessary actions to determine whether the packaging for a given dietary supplement meets specifications so that the condition of the packaging will ensure the quality of your product (21 CFR 111.410(a));
- Control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies; however, label reconciliation is not required for cut or rolled labels if a 100 percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations (21 CFR 111.410(b));
- Examine packaging and labels for each batch of dietary supplement, before conducting packaging and labeling operations, to determine whether the packaging and labels conform to the master manufacturing record (21 CFR 111.410(c)); and
- Be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution (21 CFR 111.410(d)).

### 2. **Does the DS CGMP rule require me to place a batch, lot, or control number on the packaged and labeled dietary supplement?**

No. Putting a batch, lot, or control number on the packaged and labeled dietary supplement is one way to satisfy the requirement in 21 CFR 111.410(d) that you be able to determine the complete manufacturing history and control of the packaged and labeled dietary supplement through distribution. However, you have flexibility to develop and use other mechanisms to satisfy this requirement. For example, if you make one type of product

that you distribute to a select few customers, you may be able to trace the dietary supplement using dates on distribution records to such customers, by using different containers, or by labeling other than a batch, lot, or control number affixed to the label.

(72 FR 34752 at 34900)

**3. What does the DS CGMP rule require me to do regarding filling, assembling, packaging, labeling, and related operations?**

The DS CGMP rule requires you to fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record, using any effective means, including:

- Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary supplement packaging, as appropriate (21 CFR 111.415(a));
- Protecting manufactured dietary supplements from contamination, particularly airborne contamination (21 CFR 111.415(b));
- Using sanitary handling procedures (21 CFR 111.415(c));
- Establishing physical or spatial separation of packaging and label operations from operations on other components and dietary supplements to prevent mix-ups (21 CFR 111.415(d));
- Identifying, by any effective means, filled dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mix-ups (21 CFR 111.415(e));
- Assigning a batch, lot, or control number to each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement and each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling (21 CFR 111.415(f));
- Examining a representative sample of each batch of the packaged and labeled dietary supplement to determine whether the dietary supplement meets specifications established in accordance with 21 CFR 111.70(g) (21 CFR 111.415(g)); and
- Suitably disposing of labels and packaging for dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and label operations (21 CFR 111.415(h)).

**4. When may I repackage or relabel a dietary supplement?**

You may repackage or relabel a dietary supplement only after quality control personnel have approved such repackaging or relabeling.

(21 CFR 111.420(a))

**5. What does the DS CGMP rule require me to do regarding repackaging and relabeling?**

The DS CGMP rule requires that:

- You examine a representative sample of each batch of repackaged or relabeled dietary supplements to determine whether the repackaged or relabeled dietary supplements meet all required specifications (21 CFR 111.420(b)); and
- Quality control personnel approve or reject each batch of repackaged or relabeled dietary supplement prior to its release for distribution (21 CFR 111.420(c)).

**6. What does the DS CGMP rule require me to do with a packaged and labeled dietary supplement that is rejected for distribution?**

The DS CGMP rule requires you to clearly identify, hold, and control under a quarantine system for appropriate disposition any packaged and labeled dietary supplement that is rejected for distribution.

(21 CFR 111.425)

## **XVII. Subpart M - Holding and Distributing**

**1. What does the DS CGMP rule require me to do when holding components, dietary supplements, packaging, and labels?**

The DS CGMP rule requires you to:

- Hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and dietary supplements are not affected (21 CFR 111.455(a));
- Hold packaging and labels under appropriate conditions so that the packaging and labels are not adversely affected (21 CFR 111.455(b));
- Hold components, dietary supplements, packaging, and labels under conditions that do not lead to the mix-up, contamination, or deterioration of components, in-process materials, dietary supplements, packaging, and labels (21 CFR 111.455(c));

**2. What does the DS CGMP rule require me to do when holding in-process materials?**

The DS CGMP rule requires you to:

- Identify and hold in-process material under conditions that protect against mix-up, contamination, and deterioration (21 CFR 111.460(a)); and
- Hold in-process material under appropriate conditions of temperature, humidity, and light (21 CFR 111.460(b)).

**3. What container-closure system does the DS CGMP rule require me to use to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to use the following container-closure systems to hold reserve samples of dietary supplements:

- If you are distributing a packaged and labeled dietary supplement, the DS CGMP rule requires you to keep the reserve samples in a container-closure system that is the same as the container-closure system in which the dietary supplement is distributed.
- If you are distributing a dietary supplement for packaging and labeling, the DS CGMP rule requires you to keep the reserve samples in a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which you distributed the dietary supplement for packaging and labeling elsewhere. For example, if you distribute product in bulk using a polyethylene bottle that can hold 50 kilograms of the product, and there is an air space above the product, you would hold the reserve samples in a polyethylene bottle with an air space. However, you would use a bottle sized to fit the smaller amount you are holding in reserve.

(21 CFR 111.83(b)(1); 21 CFR 111.465(a)(2); 72 FR 34752 at 34904)

**4. How does the DS CGMP rule require me to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to hold reserve samples under conditions consistent with product labels or, if no storage conditions are recommended on the label, under ordinary storage conditions. For example, if the product label states "Keep this product refrigerated," you would store the reserve sample in a refrigerator.

(21 CFR 111.465(a)(1))

**5. How long does the DS CGMP rule require me to hold reserve samples of packaged and labeled dietary supplements?**

The DS CGMP rule requires you to hold reserve samples of packaged and labeled dietary supplements for:

- One year past the shelf life date (if shelf life dating is used); or
- Two years from the date of distribution of the last batch of dietary supplements associated with the reserve sample.

(21 CFR 111.83(b)(3) and 111.465(b))

**6. What does the DS CGMP rule require me to do when distributing dietary supplements?**

The DS CGMP rule requires you to distribute dietary supplements under conditions that will protect the dietary supplements against contamination and deterioration.

(21 CFR 111.470)

## **XVIII. Subpart N - Returned Dietary Supplements**

**1. What does the DS CGMP rule require me to do with a returned dietary supplement?**

The DS CGMP rule requires you to identify and quarantine a returned dietary supplement until quality control personnel conduct a material review and make a disposition decision.

(21 CFR 111.510)

**2. When does the DS CGMP rule require me to destroy, or otherwise suitably dispose of, a returned dietary supplement?**

The DS CGMP rule requires you to destroy, or otherwise suitably dispose of, any returned dietary supplement unless the outcome of a material review and disposition decision is that quality control personnel approve the salvage of the returned dietary supplement for redistribution, or approve the returned dietary supplement for reprocessing.

(21 CFR 111.515)

**3. When may I salvage a returned dietary supplement?**

You may salvage a returned dietary supplement only if quality control personnel conduct a material review and make a disposition decision to allow the salvage.

(21 CFR 111.520)

**4. What does the DS CGMP rule require me to do with a returned dietary supplement that quality control**

### **personnel approve for reprocessing?**

The DS CGMP rule requires that:

- You ensure that any returned dietary supplements that are reprocessed meet all product specifications established for the finished batch to ensure the quality of the dietary supplement (21 CFR 111.525(a)); and
- Quality control personnel approve or reject the release for distribution of any returned dietary supplement that is reprocessed (21 CFR 111.525(b)).

### **5. When does the DS CGMP rule require me to conduct an investigation of my manufacturing processes and other batches following the return of a product?**

The DS CGMP rule requires you to conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications if the reason for a dietary supplement being returned implicates other batches.

(21 CFR 111.530)

## **XIX. Subpart O - Product Complaints**

### **1. What are some examples of product complaints?**

Examples of product complaints are: foul odor, off taste, illness or injury, disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, mislabeling, or dietary supplements that are superpotent, subpotent, or contain the wrong ingredient, or contain a drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead).

(21 CFR 111.3)

### **2. Does the DS CGMP rule establish requirements for handling complaints about the inherent safety of a dietary supplement?**

No (72 FR 34752 at 34763 and 34765). However, we encourage firms to investigate all complaints in a consistent way, regardless of whether the complaints relate to the quality of the dietary supplement or to the inherent safety of a dietary ingredient (72 FR 34752 at 34910). We also note that manufacturers, packers, and distributors whose names appear on the label of dietary supplements marketed in the United States are required to submit to FDA any report received of a serious adverse event associated with such dietary supplement when used in the United States (section 761 of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 379aa-1)) (see also question 8 below).

### **3. What does the DS CGMP rule require me to do during the review and investigation of a product complaint?**

The DS CGMP rule requires that:

- A qualified person review all product complaints to determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury (21 CFR 111.560(a)(1));
- A qualified person investigate the product complaint if it is determined that the product complaint does involve such a failure (21 CFR 111.560(a)(2));
- Quality control personnel review and approve decisions about whether to investigate a product complaint and review and approve the findings and follow-up action of any investigation performed (21 CFR 111.560(b)); and
- The review and investigation of the product complaint extend to all relevant batches and records (21 CFR 111.560(c)).

### **4. Am I subject to the requirements for product complaints if I am a packager, labeler, or distributor rather than a manufacturer?**

Yes. The DS CGMP rule requires any person in the manufacturing chain who receives a product complaint to comply with the requirements for product complaints (21 CFR 111.1; 72 FR 34752 at 34909). This is true regardless of the source of the product complaint – i.e., regardless of whether you receive the complaint from a consumer or from another firm in the manufacturing chain (72 FR 34752 at 34909).

### **5. What should I do if I am a packager, labeler, or distributor and I conclude that the problem in a product complaint is unrelated to any process under my control?**

We recommend that you contact the manufacturer so that the manufacturer can determine whether the product complaint involves a possible failure of a dietary supplement to meet any of its specifications, or any other requirements of part 111, including those specifications and other requirements that, if not met, may result in a risk of illness or injury.

(72 FR 34752 at 34909)

**6. Am I subject to the requirements for product complaints if I manufacture dietary ingredients rather than dietary supplements?**

You are not subject to the requirements for product complaints if you manufacture dietary ingredients and do not sell the dietary ingredients directly to consumers (72 FR 34752 at 34791). However, if you are a manufacturer of dietary ingredients, and you receive complaints about a dietary supplement, we recommend that you share those complaints with those in the manufacturing chain associated with that dietary supplement's manufacture so others may take corrective action as needed (72 FR 34752 at 34798). In addition, we encourage you to evaluate the complaint to determine if it may involve a problem with the manufacture of the dietary ingredient (72 FR 34752 at 34792).

**7. Does the DS CGMP rule require me to report any product complaints to FDA?**

No. The DS CGMP rule addresses the internal processes and controls that persons who manufacture, package, label, or hold dietary supplements must follow rather than any procedures for reporting any product complaints to us (72 FR 34752 at 34909). However, we recommend that firms who receive product complaints notify us about any illness or injury, because, for example, we may have additional expertise or data that may be helpful in investigating the complaint or determining whether the problem applies to more than one product. We encourage you to include this recommendation in the written procedures you develop for handling product complaints (72 FR 34752 at 34909). Information about how to notify us about a product complaint is available on our Internet site (Ref. 2).

**8. What should I do if I receive a product complaint involving serious illness or injury?**

We encourage firms who receive a product complaint involving serious illness or injury to consult with a health care provider and to include such a consultation in its written procedures for handling product complaints (72 FR 34752 at 34909). In addition, be advised that in 2006 Congress enacted the "Dietary Supplement and Non-Prescription Drug Consumer Protection Act" (Pub. L. 109-462), which established a new statutory requirement for mandatory reporting to FDA of serious adverse events (section 761 of the Act (21 U.S.C. 379aa-1)). This law defines "serious adverse events" as those adverse events that result in death, a life-threatening experience, an inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or that require medical or surgical intervention to prevent such serious outcomes (based on reasonable medical judgment). Among other things, this law also has specific provisions for how serious adverse event reports are to be submitted to FDA and recordkeeping requirements relating to adverse event reports. We encourage firms who are unsure as to whether an adverse event should be reported to FDA to contact us for assistance (72 FR 34752 at 34909). FDA has also published guidance for industry about mandatory dietary supplement adverse event reporting and recordkeeping requirements, entitled "Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act," (Ref. 3).

## **XX. Subpart P – Records and Recordkeeping**

**1. What does the DS CGMP rule require regarding the records that I make and keep?**

The DS CGMP rule requires that:

- You keep written records for one year past the shelf life date (if shelf life dating is used), or for 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records (21 CFR 111.605(a));
- Records be kept as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records (21 CFR 111.605(b)); and
- All electronic records comply with 21 CFR part 11 (21 CFR 111.605(c)).

**2. What does the DS CGMP rule require me to do to make records available to FDA?**

The DS CGMP rule requires you to:

- Have all required records, or copies of such records, readily available during the retention period for inspection and copying by FDA when requested (21 CFR 111.610(a)); and
- Make suitable reader and photocopying equipment readily available to FDA if you use reduction techniques such as microfilming (21 CFR 111.610(b)).

## **XXI. References**

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of November 9, 2010, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance.

1. FDA. [Guidance for Industry: Product Recalls, Including Removals and Corrections](#)<sup>2</sup>.
2. FDA. [Report a Problem. How to Report Problems With Products Regulated by FDA](#)<sup>3</sup>.

3. [FDA. Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act<sup>4</sup>.](#)

<sup>1</sup>.This guidance has been prepared by the Division of Dietary Supplement Programs in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

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