# XII. Comments on the Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product that You Receive for Packaging or Labeling as a Dietary Supplement (Final Subpart G)

## A. Organization of Final Subpart G

In the 2003 CGMP Proposal, the requirements for production and process controls related to components, packaging, dietary ingredients, labels, and dietary supplements that you receive were set forth in proposed § 111.40. As shown in table 8, we are reorganizing the requirements related to components, packaging, labels, and product that you receive for packaging and labeling as a dietary supplement, into a distinct subpart (final Subpart G - Production and Process Control System: Requirements for Components, Packaging, and Labels, and for Product that You Receive for Packaging or Labeling as a Dietary Supplement). Table 8 lists the sections in final subpart G and identifies the sections in the 2003 CGMP Proposal that form the basis of the final rule.

Table 8. - Derivation of Sections in Final Subpart G

| Final Rule | 2003 CGMP Proposal |
|---|---|
| § 111.153 What Are the Requirements Under this Subpart for Written Procedures? | N/A |
| § 111.155 What Requirements Apply to Components of Dietary Supplements? | § 111.40(a)(1) through (a)(5) |
| § 111.160 What Requirements Apply to Packaging and Labels Received? | § 111.35(e)(4)<br>§ 111.40(a)(2)<br>§ 111.40(b) |
| § 111.165 What Requirements Apply to a Product Received for Packaging or Labeling as a Dietary Supplement (and for Distribution Rather Than for Return to the Supplier)? | § 111.40(a) |
| § 111.170 What Requirements Apply to Rejected Components, Packaging, and Labels, and to Rejected Product That are Received for Packaging or Labeling as a Dietary Supplement? | § 111.74 |
| § 111.180 Under this Subpart, What Records Must You Make and Keep? | § 111.40(c)(1)(i) through (c)(1)(iv)<br>§ 111.40(c)(2) |

## B. Highlights of Changes to the Proposed Requirements for Components, Packaging, and Labels, and Product That You Receive for Packaging or Labeling as a Dietary Supplement

1. Revisions

The final rule:

- Applies to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in § 111.1.
- Includes requirements that apply to components, including components that are dietary ingredients, regardless of whether you receive the components or manufacture them yourself (final §§ 111.70(b) and 111.75(a)).
- Separates the requirements for product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)(final § 111.165) from the requirements for components (final § 111.155).

2. Changes After Considering Comments

The final rule:

- Incorporates a new requirement to establish and follow written procedures for fulfilling the requirements for components, packaging, labels, and product you receive from a supplier for packaging or labeling as a dietary supplement for distribution rather than for return to the supplier.

## C. General Comments on Proposed § 111.40

(Final Subpart G)

(Comment 236) One comment states that many companies use an electronic material resource planning system to control the status of inventory, and assert this type of system provides suitable controls to ensure only materials that are approved by the quality control unit are used. The comment notes only the quality control unit has the authority to release any material on quarantine and asks whether such a system would comply with the requirements of the proposed regulation.

(Response) Based on the limited information provided by the comment, it appears the electronic inventory system that the comment describes would comply with the requirements of final § 111.155 (c)(3) to quarantine components until the quality control unit releases them for use in manufacture, provided that appropriate controls are established and used to ensure the system functions in accordance with its intended use as required by final § 111.30(e). We are making no changes based on this comment.

## D. What Are the Requirements Under This Subpart for Written Procedures?

(Final § 111.153)

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV. We also respond to individual comments on specific provisions in the same section.

Final § 111.153 requires you to establish and follow written procedures for fulfilling the requirements of Subpart G. Under final § 111.180(b)(1), as a conforming requirement, we require you to make and keep records of such written procedures. Such records would be available to us under the requirements in subpart P, Records and Recordkeeping.

## E. What Requirements Apply to Components of Dietary Supplements? (Final § 111.155)

The final rule applies only to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion under final § 111.1. The effect of this revision is that the requirements that derive from proposed § 111.40(a) for components you receive now apply to all components, whether you receive them or manufacture them yourself.

The final rule separates the requirements for product you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)(final § 111.165) from the analogous requirements for components, packaging, and labels (final § 111.155).

1. Proposed § 111.35(d)

In proposed § 111.35(d), we would require that any substance, other than a "dietary ingredient" within the meaning of section 201(ff) of the act, that is subject to section 409 of the act, be: (1) Authorized for use as a food additive under section 409 of the act; or (2) authorized by a prior sanction consistent with § 170.3(l); or (3) if used as a color additive, subject to a listing that, by the terms of that listing (including a listing for use in coloring foods generally), includes the use in a dietary supplement; or (4) GRAS for use in a dietary supplement. We also proposed that any claim that a substance is GRAS must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary supplement. Further, under § 111.35(d)(5), we proposed to require that you comply with all other applicable statutory

and regulatory requirements under the act.

We received several comments objecting to one or more of the provisions of proposed § 111.35(d) and to our statement in the preamble to the 2003 CGMP Proposal regarding how we would apply the provisions of proposed § 111.35(d)(4). After considering these comments, we have deleted the requirements in § 111.35(d) in this final rule.

(Comment 237) Several comments recommend proposed § 111.35(d) be deleted because the statute already requires that ingredients, other than "dietary ingredients," be approved as a food additive or a color additive, or be GRAS. Some comments assert that proposed § 111.35(d) and proposed § 111.5 already require compliance with all other applicable statutory and regulatory requirements under the act, and therefore, there is no need to refer to food additive, color additive, and GRAS requirements. Some comments assert that proposed § 111.35(d) is unnecessary because there is no such requirement in the food CGMPs. Other comments assert this proposed requirement should be deleted because it is only tangentially related to the manufacturing process, and CGMP should be focused on setting minimum standards for manufacturing systems and steps in the

production and distribution of dietary supplements that are required to produce safe and accurately labeled products. Other comments assert that because the drug CGMPs do not have such a requirement, dietary supplement CGMPs should not have such a requirement.

Other comments did not object to the principle underlying proposed § 111.35(d), ***i.e.***, that we need to ensure GRAS substances used in dietary supplements are GRAS under the manufacturer's specified use. However many comments disagreed, for various reasons, with the proposed requirement in § 111.35(d)(4) that a claim that a substance is GRAS must be supported by a citation to our regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary supplement.

(Response) We agree that proposed § 111.35(d) is unnecessary because there are already existing statutory and regulatory requirements related to the lawful use of ingredients used in dietary supplements. We do not have to repeat those requirements in this final rule. Ensuring the ingredients you use to manufacture a dietary supplement are lawful under the

applicable statutory and regulatory requirements is the responsibility of the dietary supplement manufacturer.

For the reasons set forth above, we are deleting proposed § 111.35(d)(4) from the final rule. Because we are deleting this provision, it is unnecessary to respond to the various comments related to the documentation that proposed § 111.35(d)(4) would have required, or whether we could not have included such requirements in the dietary supplement CGMP final rule because the requirements are not in food or drug CGMP regulations.

We also agree that proposed § 111.35(d)(5) is redundant with § 111.5 and are therefore deleting § 111.35(d)(5) from the final rule.

Although we are deleting § 111.35(d) from the final rule, there were several comments that we received, and respond to below, that seemed to question whether existing statutory and regulatory requirements apply to the use of ingredients in a dietary supplement.

(Comment 238) One comment suggests components not found in finished goods in a material amount should not be subject to the

same GRAS requirements as those found in a material amount. Another comment states dietary supplements are excluded from the food additive definition in section 201(s) of the act, and that components that constitute the dietary supplement are also excluded from the food additive definition. The comment suggests that, under proposed § 111.35(d), we are erroneously trying to maintain food additive authority for dietary supplements.

(Response) The assertion that dietary supplements and all of their components are not subject to the food additive provisions of the act's definition is incorrect. We do maintain authority over the use of certain substances, as color additives, food additives[1], or GRAS substances that may be used in manufacturing dietary supplements.

The food additive definition in section 201(s) of the act excludes "an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement." Thus, a "dietary ingredient" described in section 201(ff)(1) of the act is not a "food additive." Nor can the use of a dietary ingredient be

[1] Although we refer to the term "food additive" in the preamble, the reader should also consider color additives and substances prior sanctioned for such use as being relevant to the discussion.

considered to be GRAS, since the GRAS status itself is an exception to the definition of a food additive. However, ingredients that may be used in a dietary supplement, other than those excepted in section 201(s), are subject to our regulatory authority as a food additive, unless their use is GRAS or authorized by a prior sanction. Thus, it is incorrect to say, as the comment asserts, that dietary supplements and all of their components are not subject to the food additive definition.

We also disagree that components not found in finished goods in a material amount should not be subject to the same GRAS requirements as those found in a material amount. It is not clear what the comment meant by "material amount." A substance that is subject to FDA's authority as a food additive is one the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of a food or that otherwise affects the characteristics of any food, if the use of such substance is not GRAS.[2] We have discretion to determine whether an ingredient is

[2] It is important to note that it is the use of the substance, not the substance itself that must be GRAS. The amount of a substance in the food is a critical factor in determining whether the use would be GRAS.

one where the agency would find the presence to be "de minimis" (*Monsanto* v. *Kennedy*, 613 F.2d 947, 956 (D.C. Cir. 1979). However, whether the agency would find it appropriate to exercise such discretion with respect to the use of a particular ingredient is beyond the scope of this final rule.

(Comment 239) Several comments questioned whether certain ingredients would be considered GRAS. One comment stated excipients regularly used in pharmaceuticals for many years and safely used in dietary supplements may not be considered GRAS for use in foods, approved for use as a food additive, or considered a dietary ingredient. An example provided was "croscarmellose sodium" used for disintegration. The comment asks permission to use any recognized excipient, an excipient that is monographed in a recognized compendium, used in drug products, or shown to be in use prior to the implementation of the final rule. Other comments stated proposed § 111.35(d) would be overly burdensome since many ingredients are GRAS for broad food use, have been used in dietary supplements without specific recognition as a GRAS use, and should be permitted. Other comments state substances listed in the USP National Formulary, Food Chemical Codex, the American Pharmaceutical

Associations Handbook of Pharmaceutical Excipients, and FDA's inactive ingredient guide are considered GRAS based on a history of common use even though there is no listing of these substances as GRAS.

(Response) The GRAS status of specific uses of excipients cannot be treated as a general class and is beyond the scope of this final rule. It is possible that the data needed to support safe uses as an excipient in a drug may be widely known among experts and form a basis for a consensus that use in a dietary supplement is safe. However, use of drugs containing the excipient may be short term or may be intermittent, leading to far less exposure than routine use in some dietary supplements. As human exposure increases, not only does the safety profile of the intended excipient become more important, but the purity specifications also become more critical. We advise persons who need more information about the basis for concluding that a use of a substance is GRAS to consult § 170.30 and our 2003 CGMP Proposal to establish a notification program for the use of GRAS substances (62 FR 18937, April 17, 1997).

(Comment 240) Some comments assert it is not feasible to require that starting materials used by bulk ingredient

manufacturers be GRAS or approved food additives. The comments state many ingredients are not food grade substances or approved for use in food until after processing. One comment states raw materials may become dietary ingredients after processing, but the materials from which the dietary ingredient is derived are not considered to be a GRAS ingredient, a dietary ingredient, or a dietary supplement. The comment gives examples of Ginkgo biloba leaves or Saw palmetto or cartilage. The comment asks us to consider natural products (from animal, mineral, or vegetable origin) to be included in the rule as potential raw materials for nutritional supplements. Another comment expresses concern that a soy isolate, from which natural vitamin E is derived, would not be considered a GRAS substance.

(Response) These comments seem to be concerned about the regulatory status of substances used as raw materials in the manufacture of a dietary ingredient or dietary supplement. An important consideration, however, is whether such materials become a component of the dietary ingredient or dietary supplement.

Dietary ingredient manufacturers who manufacture dietary ingredients for further processing by another person into a

dietary supplement are outside the scope of this final rule. However, such manufacturers are still subject to other applicable statutory and regulatory provisions. For example, if you are a dietary ingredient manufacturer that uses a material in the manufacture of a dietary ingredient, and the material becomes part of the dietary ingredient, we would consider it to be part of the dietary ingredient and subject to the exception to the food additive definition in section 201(s)(6) of the act. However, because the material becomes a component of the dietary ingredient, you are subject to the applicable statutory and regulatory requirements that would apply to the dietary ingredient, including the safety of the dietary ingredient.

If you use a material, other than a dietary ingredient, in the manufacture of a dietary supplement, that becomes a part of the dietary supplement, you are subject to the applicable statutory and regulatory requirements that apply to the use of such material, including its safety for such use. In this case, the use of the material would be subject to regulation as a food additive (unless it is GRAS or prior-sanctioned).

Alternatively, if you use material in the manufacture of a dietary ingredient or a dietary supplement that does not become

part of the dietary ingredient or dietary supplement, then we would not consider the material to be a food.

(Comment 241) Several comments state the color additive provision would be too restrictive if it only allowed colors listed for use in a dietary supplement, rather than colors listed for use in foods generally. Some comments note none of the color additives currently approved generally for "food" use is approved specifically for dietary supplements within the food category. Another comment argues we gave no rationale for requiring a categorical listing under specific color additives for dietary supplements. The comment states color additives are not used in any greater amount in supplements than in foods and, if anything, are probably used less because supplements are consumed in smaller amounts than foods and less color additive must be used to achieve the desired effect. One comment notes it was not familiar with any evidence to indicate that a color additive (whether it is certified or exempt) found by us to be safe for use in foods is not safe in dietary supplements.

(Response) We acknowledge that the combination of proposed § 111.35(d)(3) and several color additive listings is confusing and could lead to incorrect conclusions about whether specific

color additives may lawfully be used in a dietary supplement. As the comments point out, some listings for color additives (such as for the certified colors FD&C Blue No. 1 (§ 74.101) and FD&C Red No. 40 (§ 74.340)) list the color additive "for coloring foods (including dietary supplements) generally" - i.e., the listings specifically identify dietary supplements as a food category in which the color additive may be used. In contrast, some listings for color additives (such as for annatto extract (§ 73.30) and for beta-carotene (§ 73.95)) list the color additive "for coloring foods generally" - i.e., without specifically identifying dietary supplements as a food category in which the color additive may be used. In general, the terms of either of these two kinds of listings (i.e., "for coloring foods (including dietary supplements) generally" and "for coloring foods generally" mean we saw no need for restriction of the use of the color additive when FDA approved the listing of that color additive. Thus, a color additive listed for use in food generally may be used in a dietary supplement.

Although most listings of color additives provide for the use of the color additive in food generally, some listings for color additives restrict the use of the color additive in terms

of the food category in which it may be used. For example, under § 73.125 sodium copper chlorophyllin may be safely used to color citrus-based dry beverage mixes in an amount not exceeding 0.2 percent in the dry mix, and the terms of this listing would not include the use in a dietary supplement. We list a color additive with restrictions such as these when for example, the person who submits a petition for us to approve the listing of a color additive only requests a specific use, or when the available data and information only support the safety of a limited consumption of the color additive.

2. Final § 111.155(a)

Final § 111.155(a) (proposed § 111.40(a)(1)) requires you to visually examine each immediate container or grouping of immediate containers in a shipment you receive for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components. Final § 111.155(a) is substantially similar to proposed § 111.40(a)(1) which would require you, for components you receive, to visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals

to determine whether the container condition has resulted in contamination or deterioration of the components. Because you do not receive shipments for components you make, we are revising proposed § 111.40(a) so that it applies only to shipments of components you receive. We have added the word "immediate" to identify the container as the one in contact with the dietary supplement or component. We also have changed "has resulted" to "may have resulted" since in some cases you may not be able to make a final determination from a visual inspection alone whether the container condition has resulted in contamination or deterioration of the components.

(Comment 242) One comment supports the proposed requirements of proposed § 111.40(a) as an effective guideline for the inspection of purchased ingredients.

(Response) The provisions of final § 111.155(a) are requirements, not guidelines, as stated by the comment.

3. Final § 111.155(b)

Final § 111.155(b) (proposed § 111.40(a)(2)) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment you receive to ensure that the components are consistent with your purchase order. Final §

111.155(b) is substantially similar to proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to ensure the components are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met. As with final § 111.155(a), final § 111.155(b) clarifies that the invoice, guarantee, or certification comes in the shipment you receive.

Final § 111.155(b) does not include any requirements related to testing components. Final § 111.75(a) sets forth the requirements to test or examine components; final §§ 111.110 and 111.120 set forth requirements for the quality control unit to ensure that appropriate tests or examinations are conducted; review the results of any tests or examination;, determine whether components conform to specifications; and approve the components before they are used in the manufacture of a dietary supplement. Given this set of requirements, it would be redundant to set forth requirements regarding testing for components in final subpart G.

We did not receive comments specific to the requirements of proposed § 111.40(a)(2).

4. Final § 111.155(c)

Final § 111.155(c) (proposed § 111.40(a)(3)) requires you to quarantine components before you use them until:

(1) You collect representative samples of each unique lot of components (and, for components that you receive, of each unique shipment, and of each unique lot within each unique shipment);

(2) The quality control unit reviews and approves the results of any test or examinations conducted on components; and

(3) The quality control unit approves the components for use in the manufacture of a dietary supplement, including approval of any treatment (including in-process adjustments) of components to make them suitable for use in the manufacture of a dietary supplement, and releases them from quarantine.

Final § 111.155 modifies proposed § 111.40(a)(3) which would require:

- You to quarantine components until your quality control unit reviews the suppliers invoice, guarantee, or certification;
- The quality control unit to perform testing, as needed, of a representative sample to determine that specifications are met;
- You to conduct a material review and make a disposition

decision if specifications are not met; and

• The quality control unit to approve and release the components from quarantine before you use them.

Final § 111.155(c) includes revisions related to the following changes to other provisions already discussed.

• Under final § 111.110 the quality control unit ensures that all appropriate tests and examinations are conducted, and reviews and approves the results of tests and examinations conducted on components, but the quality control unit is not required to conduct the tests or examinations;

• Under final § 111.80(a) we establish the convention in this final rule of referring to "each unique lot within each unique shipment" rather than "each shipment lot."

• The requirements to conduct a material review and make a disposition decision are already set forth in final §§ 111.87, 111.113, and 111.120 and, therefore, are not repeated in final § 111.155; and

• Under final § 111.90(c) any batch of dietary supplement that is reprocessed, 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 all product specifications for the dietary supplement and be approved by the quality control unit before being released for distribution.

(Comment 243) Some comments address the requirement to quarantine components before you use them and assert that it is not feasible to quarantine incoming materials in a continuous extraction and purification operation, such as one built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation. One comment explains that in such operations, quarantine and quality control approval occurs later in the process after the material has been isolated and concentrated in a stable matrix suitable for holding. One comment suggests proposed § 111.40(a)(3) state "quarantine components or dietary supplements as applicable...".

(Response) We decline to revise proposed § 111.40(a)(3) as suggested by the comments. The comment describes a situation where a manufacturer of a dietary supplement is also manufacturing a dietary ingredient or other component but only provides limited information. It appears that, however, the procedures described for quarantine of the isolated, stable matrix, with subsequent evaluation by the quality control unit

before release for use in the manufacture of the dietary supplement, would satisfy the requirements of final § 111.155(c), provided the quality control unit is able to determine that all specifications for the component are met.

(Comment 244) One comment states that plant personnel who are not formally part of the manufacturer's quality control unit can conduct the quality control functions required for the release of materials from quarantine before use.

(Response) As already discussed with respect to the definition of the quality control unit (see section VI), these comments may have misunderstood the role of the quality control unit. To clarify that role, final § 111.12(b) states you must identify a qualified person who is responsible for your quality control operations.

(Comment 245) One comment suggests components that cannot be used in a short time should be retested at least yearly.

(Response) We are making no changes to the provision after considering this comment. Whether any tests or examinations must be repeated over time, or whether the information in a certificate of analysis remains valid over time, is a matter to be decided by the manufacturer based on the established

characteristics and shelf life of the component.

5. Final § 111.155(d)

Final § 111.155(d)(1) (proposed § 111.40(a)(4)) requires you to identify each unique lot within each unique shipment of components you receive and any lot of components that 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 you manufactured and distributed. Final § 111.155(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce.

Final § 111.155(d)(1) and (2) are substantially similar to proposed § 111.40(a)(4) which would require you to identify each lot of components in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component, and the status (e.g., quarantined, approved, or rejected), and to trace the shipment lot to the dietary supplement you manufactured and distributed. Proposed § 111.40(a)(4) also would require you to use this unique

identifier whenever you record the disposition of each shipment lot received.

Final § 111.155(d)(1) and (2) include revisions associated with final § 111.80(a).

We did not receive comments specific to proposed § 111.40(a)(4).

6. Final § 111.155(e)

Final § 111.155(e)(proposed § 111.40(a)(5)) requires you to hold components under conditions that will protect against contamination and deterioration and avoid mixups.

We did not receive comments specific to proposed § 111.40(a)(5).

## F. What Requirements Apply to Packaging and Labels Received? (Final § 111.160)

1. Final § 111.160(a)

Final § 111.160(a) (proposed § 111.40(b)(1)) requires you to visually examine each immediate container or grouping of immediate containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or

deterioration of the packaging and labels. Final § 111.160(a) is similar to proposed § 111.40(b)(1) with the addition of the word "immediate" to identify the container as the container that is in contact with the packaging or labels and substituting "may have" for "has" before the word "resulted" as discussed in this section.

We did not receive comments specific to proposed § 111.40(b)(1).

2. Final § 111.160(b)

Final § 111.160(b) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment to ensure the packaging or labels are consistent with your purchase order. Final § 111.160(b) is a new requirement that is analogous to proposed § 111.40(a)(2). We are requiring in final § 111.160(b), that, as part of your visual identification, you compare what was received, based on the supplier's invoice, guarantee, or certification, with your purchase order so you can ensure your specifications for packaging and labels are met. This is consistent with what you would do with respect to components and dietary supplements you receive. Without final § 111.160(b), the review by the quality control unit under final §

111.120(a) would be a matter of performing receiving operations rather than performing quality control operations; as already discussed in this section, some comments asserted the quality control unit should focus on reviewing the work of others rather than conducting the operations themselves. Thus, final § 111.160 is consistent with these comments.

3. Final § 111.160(c)

Final § 111.160(c) requires you to quarantine packaging and labels before you use them in the manufacture of a dietary supplement until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of packaging and labels and, at a minimum, conduct a visual identification of the immediate containers and closures;

(2) The quality control unit reviews and approves the results of any tests or examinations conducted on the packaging and labels; and

(3) The quality control unit approves the packaging and labels for use in the manufacture of a dietary supplement and releases them from quarantine.

Final § 111.160(c) is similar to proposed §

111.40(b)(2)which would require that:

- You quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met;
- You conduct at least a visual identification of the containers and closures;
- If specifications are not met, you conduct a material review and make a disposition decision; and
- Your quality control unit approve and release packaging and labels from quarantine before you use them.

Final § 111.160(c) includes revisions that reflect the following change already discussed in this final rule:

- Referring to “each unique lot within each unique shipment” rather than “each shipment lot;”

We did not receive comments specific to proposed § 111.40(b)(2).

4. Final § 111.160(d)

Final § 111.160(d)(1) 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 you distributed. Final § 111.160(d)(2) requires you use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of packaging and labels. Final § 111.160(d) derives from proposed § 111.40(b)(3) which would require you to identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(b)(3) also would require that you use this unique identifier whenever you record the disposition of each shipment lot received.

Final § 111.160(d) includes revisions that reflect the following changes already discussed in this final rule:

- Reference to "each unique lot within each unique shipment" rather than "each shipment lot."
- As a clarification, final § 111.160(d)(2) refers to the "dietary supplement that you distributed" rather than to the "dietary supplement manufactured and distributed" to avoid a

narrow - and incorrect - interpretation of "manufactured." Under proposed § 111.40(b)(3) we used the term "manufactured" in a broad sense that includes any aspect of the manufacturing process rather than a narrow sense that applied to manufacturing operations for producing a batch of dietary supplement. Both proposed § 111.40(b)(3) and final § 111.160(e) address the need to trace the packaging and labels that you use to the product that you distribute, regardless of whether your role in the manufacturing process includes the production of the batch or includes only packaging a dietary supplement you receive from a supplier.

(Comment 246) One comment believes packaging and labels are rarely the source of quality problems. This comment suggests proposed § 111.40(b)(3) allow the use of packaging approved by the quality control unit without the need to use a specific lot identification number. The comment explains that this type of flexibility is needed when they have dozens of short run lots each day and use less than a carton of packaging supplies for each run.

(Response) This comment may have misinterpreted proposed § 111.40(b)(3). Under proposed § 111.40(b)(3) (final

§ 111.160(d)) you must assign the identifier to each unique lot within each unique shipment of packaging and labels when you receive them rather than each time that you use them. This number would stay the same for each of the short runs described by the comment. We are making no changes to the requirement.

5. Final § 111.160(e)

Final § 111.160(e) requires you to hold packaging and labels under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.160(e) is identical to proposed § 111.40(b)(4).

We did not receive comments specific to proposed § 111.40(b)(4).

## G. What Requirements Apply to Product That You Receive for Packaging or Labeling as a Dietary Supplement? (Final § 111.165)

Final § 111.165 (proposed § 111.40(a)) sets out actions you must take when you receive a product for packaging and labeling and for distribution. Final § 111.165 includes editorial changes associated with the reorganization and revisions that reflect changes we are making to other sections of the final

rule.

Final § 111.165 sets forth requirements for "product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)" rather than for "dietary supplements that you receive."

The final rule separates the requirements in proposed § 111.40(a) for product that you receive from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.165) from the analogous requirements for components, packaging, and labels (final § 111.155).

1. Final § 111.165(a)

Final § 111.165(a) requires you to visually examine each immediate container or grouping of immediate containers in a shipment of product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product. Final § 111.165(a) is substantially

similar to proposed § 111.40(a)(1) which, in part, would impose this requirement for dietary supplements you receive. We have added the word "immediate" to identify the container as the container that is in contact with the product you receive for packaging or labeling as a dietary supplement and substituted "may have" for "has" before the word "resulted" as explained in this section.

2. Final § 111.165(b)

Final § 111.165(b) requires you to visually examine the supplier's invoice, guarantee, or certification in a shipment of the received product to ensure the received product is consistent with your purchase order. Final § 111.165(b) is substantially similar to proposed § 111.40(a)(2) which, in part, would establish a similar requirement for dietary supplements that you receive.

3. Final § 111.165(c)

Final § 111.165(c) requires you to quarantine the received product until:

(1) You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product;

(2) The quality control unit reviews and approves the documentation to determine whether the received product meets the specifications you established under § 111.70(f); and

(3) The quality control unit approves the received product for packaging or labeling as a dietary supplement and releases the received product from quarantine.

Final § 111.165(c) is similar to proposed § 111.40(a)(3) which, in part, would require that:

- You quarantine dietary supplements that you receive until your quality control unit reviews the suppliers invoice, guarantee, or certification;
- The quality control unit performs testing, as needed, of a representative sample to determine that specifications are met;
- You conduct a material review and make a disposition decision if specifications are not met; and
- The quality control unit approves and releases the dietary supplements that you receive from quarantine before you use them.

Final § 111.165(c) includes revisions that reflect that under final § 111.75(e) before you package or label a product you received for packaging or labeling as a dietary supplement,

you must visually examine the product and have documentation to determine whether the specifications you established under § 111.70(f) are met, but not otherwise examine or conduct tests.

4. Final § 111.165(d)

Final § 111.165(d)(1) requires that you 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. Final § 111.165(d)(2) requires you to use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product. Final § 111.165(d) derives from proposed § 111.40(a)(4) which would require you, in part, to identify each lot of dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the dietary supplement, and the status (*e.g.*, quarantined, approved, or rejected) and to trace the shipment lot to the dietary supplement manufactured and distributed. Proposed § 111.40(a)(4) also would require you to use this

identifier whenever you record the disposition of each shipment lot received.

Final § 111.165(d) includes a revision associated with final § 111.80 referring to "each unique lot within each unique shipment" rather than "each shipment lot."

5. Final § 111.165(e)

Final § 111.165(e) requires you to hold the received product under conditions that will protect against contamination and deterioration, and avoid mixups. Final § 111.165(e) derives from proposed § 111.40(a)(5) with editorial changes associated with the reorganization.

## H. What Requirements Apply to Rejected Components, Packaging, Labels, and to Rejected Product That You Receive for Packaging or Labeling as a Dietary Supplement?

(Final § 111.170)

Final § 111.170 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 (and for distribution rather than for return to the supplier), that is

rejected and unsuitable for use in manufacturing, packaging, or labeling operations. Final § 111.170 is substantially similar to proposed § 111.74 which would require you to clearly identify, hold, and control under a quarantine system any component, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

We did not receive comments specific to proposed § 111.74. Final § 111.170 includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture.

## I. Under this Subpart, What Records Must You Make and Keep? (Final § 111.180)

Final § 111.180 sets forth the requirements to make and keep records associated with components, packaging, labels, and product you receive for packaging and labeling as a dietary supplement. Final § 111.180 derives from proposed § 111.40(c).

1. Final § 111.180(a)

Final § 111.180(a) requires you to make and keep records required under subpart G in accordance with subpart P. Final § 111.180(a) derives from proposed § 111.40(c)(2), with editorial changes associated with the reorganization.

We did not receive comments specific to the requirements set forth in final § 111.180(a).

2. Final § 111.180(b)(1)

Final § 111.153 requires you to establish and follow written procedures to fulfill the requirements of subpart G. These written procedures are records. Therefore, final § 111.180(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart G.

3. Final § 111.180(b)(2)

Final § 111.180(b)(2) requires you to make and keep receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels, and for products you receive for packaging or labeling as dietary supplements (and for distribution rather than for return to the supplier). Final § 111.180(b)(2) derives from proposed § 111.40(c)(2) with editorial changes associated with the reorganization. Final §

111.180(b)(2) also includes revisions associated with the series of provisions that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement you manufacture. Because the final rule provides that you may rely, under certain circumstances, on a certificate of analysis to ensure that some component specifications are met (final § 111.75(a)(2)(ii)) and that you may rely, in part, on documentation to determine whether specifications for received products are met, we specifically identify a certificate of analysis and common forms of documentation as being "receiving records" for purposes of this rule.

(Comment 247) One comment on proposed § 111.40(c)(2) points out the recordkeeping requirements of any final rule will be a costly burden for a company that produces multiple ingredient products in several packaging configurations and will be much greater than the burden for a company that produces batches of single ingredient products in one packaging configuration.

(Response) We acknowledge that companies that produce

multiple ingredient products in several packaging configurations will have more records to keep than companies that produce single ingredient products in one packaging configuration. However, these records are necessary to be able to determine the source of the component, packaging, and labels, so that if adulteration of the dietary supplement occurs, the records will show the source of the material so that its use can be stopped.

4. Final § 111.180(b)(3)

Final § 111.180(b)(3) requires you to make and keep documentation that the requirements of Subpart G were met. Under final § 111.180(b)(3)(i) the person who performs the required activity must document, at the time of performance, that the required operation was performed. Under final § 111.180(b)(3)(ii), the documentation must include:

(A) the date that the components, packaging, labels, or products you receive for packaging or labeling as a dietary supplement were received;

(B) the initials of the person performing the required operation;

(C) the results of any tests or examinations conducted on components, packaging or labels, and of any visual examination

of product you receive for packaging or labeling as a dietary supplement; and

(D) any material review and disposition decision conducted on components, packaging, labels, or products received for packaging or labeling as a dietary supplement.

Final § 111.180(b)(3) differs from proposed § 111.40(c)(1)(i) through (iv), by referring to "required operation" rather than "requirement." Additionally as conforming revision associated with final § 111.75(a) which requires appropriate tests and examinations, final § 111.180(b)(3) requires you to include in the documentation the results of any examinations as well as tests. Final § 111.180(b)(3) also includes revisions associated with the series of changes that distinguish a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a dietary supplement that you manufacture.

(Comment 248) A few comments note proposed § 111.40(c) requires the signature of the person performing the requirement, whereas other sections of the 2003 CGMP Proposal, such as proposed § 111.50(c)(2), only require the initials of the person

performing the requirement. One comment requests the format for the requirement to document the person performing the step be made consistent throughout the regulations.

(Response) We agree that the identity of the person performing a requirement should be required throughout the final rule and that this can be accomplished through initials except for operations that are performed by the quality control unit. Therefore, we are revising the requirements so that a signature (and not initials) is required for any operation performed by the quality control unit (see final § 111.140). Because § 111.40(c)(1)(ii) is not a quality control operation, we also revised proposed § 111.40(c)(1)(ii) (final § 111.180(b)(3)) to require the initials, rather than the signature, of the person performing the required operation. Initials are required for other circumstances that do not involve quality control operations, including final § 111.180(b)(3). However, whenever this final rule requires initials, a signature is also acceptable, because a signature would achieve the goal of identifying the person who performed the requirement.