intended use. Although many methods that are scientifically valid have been formally validated, other methods may not have been subject to the formal validation process, e.g., by collaborative studies using multiple laboratories, but nonetheless remain scientifically valid because they are, in fact, suitable for their intended use. For this reason, we stated that the 2003 CGMP Proposal would permit tests using methods other than those that are officially validated (68 FR 12157 at 12163). Consistent with the view that we expressed in the 2003 CGMP Proposal, we believe a scientifically valid method is one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid test is one that consistently does what it is intended to do.

Under final § 111.75(h)(1), you must ensure the tests and examinations you use to determine whether the specifications are met are appropriate, scientifically valid methods. Under final § 111.75(h)(2) the tests and examinations you use must include at least one of the following: (1) Gross organoleptic analysis, (2) macroscopic analysis, (3) microscopic analysis, (4) chemical analysis, or (5) other scientifically valid methods.

(Comment 193) One comment questions how a company would know of all the available scientifically valid methods when it deals with hundreds of items. The comment states it cannot be expected to have expertise in the assay methodology for so many different ingredients.

Several comments suggest we make fuller use of available monographs and other resources on test methods and method development. These sources include USP and AHP monographs, AOAC International, the European Pharmacopoeia, and the WHO. The comments urge us to disseminate information on these additional resources.

Many comments assert that several organizations have published relevant analytical methods, such as macroscopic, microscopic, and chemical methods, that can be used in identifying herbal ingredients. These comments suggest that we should acknowledge those methods and organizations as authoritative sources of quality standards.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12209), we acknowledged that validated methods exist in official compendia for vitamins, minerals, and several botanicals, and we recommended you use validated methods whenever such methods are available. We explicitly stated that you may use validated methods that can be found in official references, such as AOAC International, USP, and others.

As discussed in this section (see response to comment 196), we believe that it is sufficient to provide in this preamble general guidance on what we consider to be scientifically valid tests, such as those based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research, and leave it to the manufacturer to decide what scientifically valid tests or examinations to use in a given operation. In the future, we may consider issuing guidance as to sources of appropriate tests or examinations, along with other guidances that we may find useful that relate to certain dietary supplement CGMP.

(Comment 194) One comment states the act prohibits us from imposing testing requirements for which scientifically valid methods are not generally available, and other comments believe that not all components have scientifically valid identification tests. Given the substantial ongoing efforts towards method development, the comments believe that the proposed requirements for testing would impose standards on many products and

ingredients that cannot be met through current and generally available methods.

(Response) We disagree that the statute prohibits us from imposing testing requirements. Section 402(g)(2) of the act states that dietary supplement CGMP regulations "may not impose standards for which there is no current and generally available analytical methodology." We are not imposing such standards. The manufacturer must establish specifications for its product and components, and we have provided flexibility for how the manufacturer can determine whether those specifications are met. The manufacturer can test, examine, rely on a certificate of analysis (other than to verify the identity of dietary ingredients), or, in the case of a specification that is exempted from periodic testing of a finished batch, rely on other information that ensures that such an exempted product specification is met.

(Comment 195) One comment requests clarification on the definition of "examination" and asks whether it includes monitoring of process parameters as established in the master manufacturing record. If so, the comment questions whether this practice would satisfy the requirement now in final § 111.75(h)(1).

(Response) Under final § 111.75(h), scientifically valid tests and examinations include techniques such as gross organoleptic analysis, macroscopic analysis, chemical analysis, and other scientifically valid methods. As discussed in the response to comment 169, monitoring in-process parameters could encompass tests such as measuring pH or viscosity. Such tests would fall under "other scientifically valid methods."

(Comment 196) One comment contends that botanical identification is largely ignored in the 2003 CGMP Proposal. The comment states that botanical

identification forms the basic foundation for botanical authenticity and that manufacturers have a legal responsibility to ensure the authenticity of claimed ingredients. The comment recommends that specific requirements for authentication of botanical ingredients be included in the final rule.

One comment points out the difficulty in identifying and analyzing all naturally occurring ingredients in herbs and plants and suggests several alternatives to testing for all such ingredients. Another comment requests that an herbal product containing 20 percent or more ethanol have relaxed testing requirements due to the bacteriostata properties of ethanol. One comment lists some alternatives for testing naturally occurring ingredients.

One comment requests clarification on the testing requirements for bovine cartilage products. The comment states there is no published method for extracting chondroitin sulfate from bovine cartilage. As a result, the comment assumes that testing for chondroitin sulfate would not be required for these products.

(Response) We believe that it is sufficient to provide in this preamble general guidance about testing, such as our discussion that scientifically valid tests include official, validated methods as well as tests based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research. It is the manufacturer's responsibility to choose which scientifically valid tests or examinations to use in a given operation. Therefore, the final rule does not address the specific testing circumstances described in these comments, such as testing requirements for an herbal product that contains 20 percent or more ethanol, or for bovine cartilage products. The manufacturer is responsible for establishing specifications and meeting such specifications, consistent with the requirements in this final rule.

In the future, we may consider issuing detailed guidance as to specific tests or examinations, along with other guidances that may be useful that relate to certain dietary supplement CGMP.

With respect to the comments that discuss botanical identification, we note that the 2003 CGMP Proposal referred to the draft report of the Dietary Supplement Working Group of FDA's Food Advisory Committee (68 FR 12157 at 12161) (Ref. 32). The draft report discusses the selection of the most appropriate and reliable identity test and the general principles for consideration in setting performance standards for such tests (Ref. 32). This report may provide useful guidance.

8. Final § 111.75(i)

Final § 111.75(i) requires you to establish corrective action plans for use when an established specification is not met. Final § 111.75(i) derives from proposed § 111.35(i)(1).

(Comment 197) One comment asks whether the proposed requirement to establish corrective action plans for use when an established specification is not met (proposed § 111.35(i)(1)) would apply to specifications for raw materials and finished goods as well as to in-process specifications.

(Response) The requirement to establish corrective action plans (final § 111.75(i)) applies to components, in-process specifications, and to the finished batch.

(Comment 198) One comment states that corrective action plans would be difficult to prepare for a variety of situations, such as for complex multivitamin and mineral formulas. One comment recommends this requirement be deleted. Another comment asserts that establishment of corrective action plans should be at the manufacturer's discretion.

(Response) We disagree that the final rule should not require you to establish corrective plans or that having such plans should be at the manufacturer's discretion. The purpose of having corrective action plans in place before a problem occurs is to help you to deal quickly and efficiently with problems as they arise.

You may have a corrective action plan to determine the steps to take if something goes wrong such as not meeting a specification. Moreover, a corrective action plan may include steps not only for dealing with an acute problem, but also for dealing with steps you would take to followup after the acute problem is resolved. For example, after you resolve an acute problem, such as a failure to meet an in-process specification, your corrective action plan may include testing of every finished batch, rather than a subset of finished batches, for some period of time to verify that the problem is resolved.

We acknowledge that it may not be practical to establish a corrective action plan for all circumstances, because not all circumstances are foreseeable. However, the comment asserting that it would be difficult to establish corrective action plans for the variety of situations that could come up for complex multivitamin and mineral formulas provided no basis for why manufacturers of such formulas could not anticipate specific situations that present potential problems.

(Comment 199) Some comments recommend that proposed § 111.35(i)(1) state "Establish procedures," rather than "Establish corrective action plans."

(Response) The comments did not explain what, if any, practical difference would exist between "procedures" and "corrective action plans." A corrective action plan is a procedure for which you must have a record in the master manufacturing record (final § 111.210(h)(5)). Because "corrective action plans"

is a term that is commonly used in the industry, we have retained it in the final rule.

*J. What Must You Do if Established Specifications Are Not Met? (Final § 111.77)*

1. Final § 111.77

As we explain in section II of this document, we reorganized the final rule to make it more "user-friendly" and to clarify the rule's applicability to certain persons, items, or activities. Final § 111.77 is a new provision that clarifies your responsibilities and identifies those responsibilities in a more "user-friendly" fashion. We have identified in final § 111.77 the consequences of not meeting the specifications you establish under subpart E and when you can consider a treatment, in-process adjustment, or reprocessing to correct a failure to meet and established specification for a component, dietary supplement, packaging, or label. Subpart F does identify these consequences in several provisions which deal with the responsibility of quality control personnel to review and approve or reject components, dietary supplements, packaging, and labels. We determined it would add clarity to state the consequences for not meeting a specification in the same subpart in which the requirements to establish specifications are located.

2. Final § 111.77(a)

Final § 111.77(a) requires that for specifications established under § 111.70(a), (b)(2), (b)(3), (c), (d), (e), and (g) that you do not meet, quality control personnel, in accordance with the requirements in subpart F of this part, must reject the component, dietary supplement, package, or label unless it approves a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished dietary supplement and that the dietary

supplement is packaged and labeled as specified in the master manufacturing record. No finished batch of dietary supplements may be released for distribution unless it complies with final § 111.123(b).

This provision identifies those specifications, if not fully met, that may be able to be corrected by treatment, in-process adjustment, or reprocessing and approved by quality control personnel. We emphasize, however, that even if, for example, corrections are approved, the finished batch of dietary supplement can not be released for distribution unless it is compliance with the requirements of final § 111.123(b) (discussed in section XI of this document).

Final § 111.77(a) derives from the following proposed provisions:

- Proposed § 111.50(d)(2), which would require the quality control unit not to approve and release for distribution any batch of dietary supplement that does not meet all specifications;
- Proposed § 111.50(f), which would require you to not reprocess a batch that deviates from the master manufacturing record unless approved by the quality control unit.
- Proposed § 111.50(g), which would require that a reprocessed batch of dietary supplement meet all specifications and that the quality control unit approve its release for distribution.
- Proposed § 111.35(i)(4)(i), which would require you, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary supplement, packaging, or label, to reject the component, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence.

- Proposed § 111.35(i)(4)(ii), which would require you, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary supplement, packaging, or label, to not reprocess a rejected component or dietary supplement unless approved by the quality control unit.

3. Final § 111.77(b)

Final § 111.77(b) requires that for specifications established under final § 111.70(b)(1) that you do not meet, quality control personnel must reject the component and the component must not be used in manufacturing the dietary supplement. Final § 111.77(b) complements final § 111.70(b)(1) which requires you to establish an identity specification for components; final § 111.75(a)(1) which requires you to conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient; and final § 111.75(a)(2) which requires you to confirm the identity of all other components. As discussed earlier in this section, many comments recommended the final rule include a requirement for an identity test of incoming components to ensure quality and safety. We agree with these comments and earlier comments that point out it may not be possible to confirm the identity of some components after they have been processed into the finished batch of the dietary supplement. For these reasons, we have concluded that, if the component specification for identity is not met, you may not use the component in the manufacture of the dietary supplement. This component specification must be met and quality control personnel are restricted in what action must be taken if this specification is not met.

4. Final § 111.77(c)

Final § 111.77(c) requires that if you do not meet the specifications established under § 111.70(f), quality control personnel must reject the product and the product must not be packaged or labeled for distribution as a dietary supplement. As with final § 111.77(b), final § 111.77(c) limits the actions you can take to package and label product you receive for packaging and labeling from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). Final § 111.77(c) complements final § 111.70(f), which requires you to establish a specification for such received product and final § 111.75(e), which requires you to visually examine the product, before you package or label it, and have documentation to determine whether the specifications that you established under § 111.70(f) are met. If you do not meet the specifications under final § 111.70(f), you must reject the product and not package or label the product for distribution as a dietary supplement.

*K. Comments on Shelf Life*

In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12203), we stated that we had considered whether to propose requirements for expiration dating, shelf life dating, or "best if used by" dating (referred to in this preamble as shelf life or expiration dating). We recognized that there are current and generally available methods to determine the expiration date of some dietary ingredients, such as vitamin C. However, we were uncertain whether there are current and generally available methods to determine the expiration dating of other dietary ingredients, especially botanical dietary ingredients. We did not propose to require expiration dating because we had insufficient scientific information to determine the biological activity of certain dietary ingredients

used in dietary supplements, and such information would be necessary to determine an expiration date. Further, because official validated testing methods (e.g., AOAC International or FDA) for dietary supplements are evolving, especially for botanical dietary ingredients, such methods are not always available to assess the strength of a dietary ingredient in a dietary supplement.

The preamble to the 2003 CGMP Proposal emphasized that, if you use an expiration date on a product, you should have data to support that date (68 FR 12157 at 12204). We recommended that you have a written testing program designed to assess the stability characteristics of the dietary supplement, and that you use the results of the stability testing to determine appropriate storage conditions and expiration dates.

In the 2003 CGMP Proposal (68 FR 12157 at 12204), we invited comment on whether any final rule should contain provisions regarding expiration dating and the feasibility of conducting tests needed to support such dates. We also invited comment on whether to require expiration dating on certain dietary ingredients and not others, for example, require expiration dating of vitamin, mineral, and amino acid, but not of botanical dietary ingredients.

(Comment 200) Several comments agree with our decision not to require expiration dating on labels for dietary supplements at this time, because of the wide range of products and the need for additional data. Most of these comments state, however, that manufacturers should be allowed to include a "best if used by" date. One comment suggests addressing the issue in a separate rulemaking. Other comments support an expiration date because consumers and retailers expect one, and some markets require one. Some

comments state that the expiration date or statement of product shelf life will help ensure that the product meets its label claims and potency.

Many comments state an expiration date on a label must be supported by a rationale or data on stability testing. Some of those comments suggest that manufacturers should have flexibility in the type of supporting data used. Although label claims should be confirmed by shelf life testing when analytical methods exist, data could come from a manufacturer's experience with the product or accelerated stability testing on similar products with the same storage container. One comment points out that some manufacturers already use stability testing. Another comment recommends that we provide a guidance document on supporting data.

One comment suggests stringent supporting data are not needed for a "best if used by" date, because that date provides a recommended time frame to ensure the best quality. Another comment asserts that the discussion about expiration dates in the 2003 CGMP Proposal gives the impression that the required level of supporting data is similar to the requirements for drug labeling, rather than the requirements for food shelf life labeling. Another comment recommends that a general maximum shelf life of 4 or 5 years should be included in the rule, with shortened or lengthened shelf lives for individual products as data become available.

(Response) These comments do not provide data or information that would reduce the uncertainty about the feasibility of conducting tests to support an expiration date and, thus, do not persuade us to alter our position not to require that you establish an expiration date for your product. Indeed, the comments generally concur with that position. Because the final rule does not require that you establish an expiration date, we decline to offer guidance on

the type of data that are acceptable to support an expiration date, other than to repeat that any expiration date that you place on a product label (including a "best if used by" date) should be supported by data.

*L. What Representative Samples Must You Collect? (Final § 111.80)*

Final § 111.80 sets forth requirements to collect representative samples of components, packaging, and labels (final § 111.80(a)); in-process materials (final § 111.80(b)); the finished batch of dietary supplement (final § 111.80(c)); product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.80(d)); and packaged and labeled dietary supplements (final § 111.80(e)). Final § 111.80(a) through (e) derive from proposed § 111.37(b)(11)(i) through (b)(11)(iv).

1. Final § 111.80(a)

Final § 111.80(a) requires you to collect representative samples of each unique lot of components, packaging, and labels that you use to determine whether the components, packaging, and labels meet specifications established in accordance with § 111.70(b) and (d), and as applicable, final § 111.70(a) (and, when you receive components, packaging, or labels from a supplier, representative samples of each unique shipment, and of each unique lot within each unique shipment). Final § 111.80(a) derives from proposed § 111.37(b)(11)(i). Final § 111.80(a) includes changes related to our review of the proposed requirements for clarity. We had used the term "shipment lot" in several proposed requirements, including § 111.35(g)(1)(i) (requirement to test components that you receive), § 111.37(b)(11)(i) (requirement to collect representative samples of components that you receive), § 111.40(a)(4) (requirements for components that you receive), § 111.40(b)(5) (requirements for packaging and labels that you receive), and § 111.50(c)(5) (requirement to

identify materials that you use in the batch production record). Some of these proposed requirements (e.g., those in §§ 111.40(a)(4) and (b)(3) and 111.50(b)(5)) make clear that you must be able to trace each lot of materials you receive to each separate shipment that contains that lot. To clarify and emphasize this meaning of shipment lot, we are revising proposed § 111.37(b)(11)(i) so that the representative samples you collect must come from "each unique shipment, and of each unique lot within each unique shipment." We make analogous revisions throughout the final rule as necessary.

As discussed in this section, final § 111.70(b) sets forth the requirements to establish specifications for components, final § 111.73 requires you to determine if the specifications established are met, and final § 111.75(a) sets forth the criteria you use to determine whether these specifications are met. Likewise, final § 111.70(f) sets forth the requirements to establish specifications 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 § 111.73 requires you to determine if specifications established are met, and final § 111.75(e) sets forth the criteria to use to determine whether these specifications are met.

For consistency with the regulations in final §§ 111.70 and 111.75, we are separating the requirement to collect representative samples of components (final § 111.80(a)) from the requirement to collect representative samples of 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.(80)(d)).

We did not receive comments specific to proposed § 111.37(b).

2. Final 111.80(b)

Final § 111.80(b) requires you to collect representative samples of 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, to determine whether the materials meet specifications established under final § 111.70(c), and, as applicable, final § 111.70(a). Final § 111.80(b) derives from proposed § 111.37(b)(11)(ii).

We did not receive comments specific to proposed § 111.37(b)(11)(ii).

3. Final 111.80(c)

Final § 111.80(c) requires you to collect representative samples of a subset of finished batches of each dietary supplement you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution, to verify that the finished batch of dietary supplement meets product specifications established in accordance with final § 111.70(e), and, as applicable, final § 111.70(a). Final § 111.80(c) derives from proposed § 111.37(b)(11)(iii). Final § 111.80(c) includes changes associated with final § 111.75(c) which provides flexibility for you to test or examine a subset of finished batches you select through a sound statistical sampling plan rather than to test or examine all finished batches. Under final § 111.75(c) the tests or examinations you conduct at the finished batch stage verify that your process is in control.

We did not receive comments specific to proposed § 111.37(b)(11)(iii).

4. Final § 111.80(d)

Final § 111.80(d) requires you to collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of

product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) to determine whether the received product meets the specifications established under final § 111.70(f), and, as applicable, final § 111.70(a). Final § 111.80(d) derives from proposed § 111.37(b)(11)(i). We did not receive comments specific to this proposed requirement. However, we are making changes to final § 111.80(d) consistent with those described for final § 111.80(a).

5. Final § 111.80(e)

Final § 111.80(e) requires you to collect representative samples of each lot of packaged and labeled dietary supplements to determine whether the packaging and labeling of the packaged and labeled dietary supplements meet specifications established in accordance with final §111.70(g), and, as applicable, final § 111.70(a). Final § 111.80(e) derives from proposed § 111.37(b)(11)(iv). Final § 111.80(e) includes revisions associated with final § 111.70(g), which requires you to establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements. Final § 111.70(g) includes specifications that determine whether you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record. Under final § 111.70(a) and (g) the parameters that we proposed to specify under proposed § 111.37(b)(11)(iv) are the required specifications for packaged and labeled dietary supplements.

Final § 111.80(e) includes a change to clarify the exact specifications by citing the relevant sections. Final § 111.80(e) also includes an editorial change in that you are required to "determine whether" specifications are met rather than to "determine that" specifications are met. We are making this change

because "determine that specifications are met" may be interpreted as a predetermined outcome, i.e., that specifications will, in fact, be met.

We did not receive comments specific to proposed § 111.37(b)(11)(iv).

*M. What Are the Requirements for Reserve Samples? (Final § 111.83)*

Final § 111.83 sets forth requirements to collect and hold reserve samples of dietary supplements. Final § 111.83 derives from proposed §§ 111.37(b)(12), 111.50, and 111.83(b)(2).

Under proposed § 111.37(b)(12) we would require holding reserve samples as an operation performed by the quality control unit. Under proposed § 111.50(h), we proposed that you collect representative reserve samples of each batch of dietary supplement. Consistent with the changes that we are making to final § 111.80, final § 111.83 does not specify who must collect and hold the required reserve samples. However, under final § 111.105(g), quality control personnel retain oversight of the collection and holding of the required reserve samples. Because the requirement to collect and hold reserve samples is not an operation that must be performed by quality control personnel, we are including the requirement to collect reserve samples in subpart E as part of the elements of a production and process control system rather than in subpart F as part of the requirements for quality control personnel.

For consistency with terms used elsewhere in the final rule, final § 111.83 requires that you "hold" reserve samples rather than "keep" them.

1. Final § 111.83(a)

Final § 111.83(a) requires you to collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute. Final § 111.83(a) derives, in part, from proposed § 111.37(b)(12), which would require the quality control unit to keep the reserve samples and, in part, from

proposed § 111.50(h), which would require you to collect representative reserve samples from each batch of dietary supplement.

(Comment 201) Several comments ask for clarification of the requirements for representative and reserve samples as proposed in § 111.37(b)(11) and (b)(12). One comment notes that proposed § 111.37(b)(11) does not indicate whether representative samples are also collected to serve as the reserve samples described in proposed § 111.37(b)(12) and asks whether the items in proposed § 111.37(b)(11)(i) through (b)(11)(iv) are to be kept as reserve samples.

(Response) As discussed in section VI of this document, we are adding a definition of "reserve sample" to reduce the potential for confusion between requirements for reserve samples and requirements for representative samples. A reserve sample is a representative sample that is held for a designated period of time.

2. Final § 111.83(b)(1)

Final § 111.83(b)(1) requires the reserve samples to be held using the same container-closure system in which the packaged and labeled dietary supplement is distributed, or if distributing dietary supplements to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which it is distributed for packaging and labeling elsewhere. Final § 111.83(b)(1) derives from proposed § 111.83(b)(2) which we proposed to include with the requirements for holding and distributing. The final sections that derive from proposed § 111.83(b)(2) are in subpart M (final § 111.465). However, we are duplicating these requirements in final § 111.83(b)(1) for clarity and ease of use, so that you have information about the requirements for the container-closure system for holding reserve samples

of packaged and labeled dietary supplements in the same section as the requirements to collect the samples.

3. Final § 111.83(b)(2)

Final § 111.83(b)(2) requires that reserve samples be identified with the batch, lot, or control number. Final § 111.83(b)(2) derives from proposed § 111.37(b)(12)(i) with editorial changes associated with the reorganization. We have added "control number" to the provision for consistency with other provisions of the final rule which refer to a "control number" in addition to a "batch or lot number."

We did not receive comments specific to proposed § 111.37(b)(12)(i).

4. Final § 111.83(b)(3)

Final § 111.83(b)(3) requires that reserve samples be retained for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of dietary supplements associated with those reserve samples, for use in appropriate investigations. Final § 111.83(b)(3) derives from proposed § 111.37(b)(12) which would require the quality control unit to keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition, as well as from proposed § 111.50(h) which would require reserve samples to be kept for 3 years from the date of manufacture. We discuss the change from 3 years to 2 years and the change from "date of manufacture" to "the date of distribution" in connection with the recordkeeping requirements in subpart P, in section XXI of this document.

Final § 111.83(b)(3) thus provides flexibility in determining how long you must hold reserve samples of packaged and labeled dietary supplements.

Final § 111.83(b)(3) does not include the proposed examples of investigations that may require the use of reserve samples because these examples are not requirements.

(Comment 202) Many comments address the requirement to keep the reserve samples after manufacture and recommend that expiration dates be a factor when determining the amount of time reserve samples should be kept and maintained. Most of the comments recommend holding reserve samples of packaged and labeled dietary supplements for 3 years from the date of manufacture or, when an expiration date has been established by the manufacturer, for 1 year after the expiration date. Other comments recommend holding reserve samples for time periods ranging from 6 months to 2 years after the expiration date.

(Response) The final rule contains requirements similar to the suggestions made by the comments. The final rule provides flexibility to hold reserve samples for 1 year past the shelf life date, when such dating is used. Any shelf life date that you include on the label of the product should be supported by data.

5. Final § 111.83(b)(4)

Final § 111.83(b)(4) requires that reserve samples consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the dietary supplement meets product specifications. Final § 111.83(b)(4) derives from proposed § 111.37(b)(12)(ii) which would require that the reserve samples consist of at least twice the quantity necessary for tests.

Final § 111.83(b)(4) provides that the reserve samples may be used for examinations or tests and to determine whether or not the dietary supplement meets product specifications, as a revision associated with final § 111.75.

(Comment 203) One comment agrees that twice the quantity necessary for testing should be collected and held.

(Response) The final rule is consistent with this comment.

*N. Who Conducts a Material Review and Makes a Disposition Decision? (Final § 111.87)*

Final § 111.87 requires quality control personnel to conduct all required material reviews and make all required disposition decisions. Final § 111.87 derives from a number of proposed requirements for conducting a material review and making a disposition (§§ 111.35(i) and (n), 111.37(b)(5) and (b)(14), 111.40(a)(3), 111.50(d)(1), and 111.85(a) and (c)). Under each of these provisions, the quality control unit would have an oversight role and would review and approve all material reviews and all disposition decisions. Under some of these provisions (i.e., §§ 111.50(d)(1) and 111.85(a) and 85(c)) the quality control unit would conduct the material review itself and make the disposition decision.

(Comment 204) One comment disagrees that the quality control unit must conduct the material review and make the disposition decision. The comment argues that manufacturing personnel are better qualified to conduct the review and make disposition decisions because they are often engineers and have the relevant expertise regarding the use of machinery and people to produce a product. In contrast, the comment asserts that quality control unit personnel generally are chemists with expertise only in testing and little expertise in manufacturing. The comment asserts that the quality control unit should not

be expected to make decisions concerning manufacturing operations; however, it should be informed of changes so it can evaluate the results of reprocessing on the finished product.

(Response) We agree, in part, with the comments and the final rule simplifies the provisions regarding a material review and disposition decision. Quality control personnel can conduct the material review and disposition decision by reviewing the underlying information gathered or obtained by other qualified personnel and then making the final decision. Under the final rule, we retain the principle that qualified individuals other than quality control personnel can contribute to the quality control personnel's material review and disposition decision. The final rule sets forth the following requirements:

- Under final § 111.87, quality control personnel must conduct all required material reviews and make all required disposition decisions;
- Under final § 111.103, you must establish and follow written procedures for conducting a material review and making a disposition decision; and
- Under final § 111.140(b)(3)(vii), documentation of a material review and disposition decision and followup must include the signature of the individual(s) designated to perform the quality control operations, who conducted the material review and made the disposition decision, and of any qualified individual who provided information relevant to that material review and disposition decision.

Taken in total, the final rule establishes a system in which you have flexibility to develop procedures that suit your organization, including having qualified individuals, other than the designated quality control personnel, provide information relevant to the material review and disposition decision.

For example, under final § 111.140(b)(3), you could have a qualified individual in the production department prepare a report that includes all the required documentation and information and provide a signed copy of that report to designated quality control personnel. An individual designated to perform quality control operations would then read that report, add to it if necessary, conduct any additional investigations if necessary, and if he or she agrees with the report, co-sign the report or an amended report that includes additional documentation or information, thus completing a material review and disposition decision.

The final rule provides for the participation of qualified individuals, other than those designated to perform quality control operations, in conducting the material review. In addition, as already discussed, under final § 111.12(b) you may assign a qualified individual who has responsibilities for operations other than quality control to perform quality control operations, provided that the individual has distinct and separate responsibilities related to performing quality control operations.

*O. What Requirements Apply to Treatments, In-Process Adjustments, and Reprocessing When There is a Deviation or Unanticipated Occurrence or When a Specification Established in Accordance with § 111.70 Is Not Met? (Final § 111.90)*

1. Final § 111.90

Final § 111.90 is a unified provision that clarifies your responsibilities regarding treatment or in-process adjustments to a component, and in-process adjustments or reprocessing of a dietary supplement, in a more "user-friendly" fashion. We have identified in one provision the restrictions that apply to these

operations. Final § 111.90 derives from proposed §§ 111.35(i)(4)(i), (i)(4)(ii), and (i)(4)(iii); 111.50(d)(1), (f), and (g); and 111.65(d).

Final § 111.90 includes the following changes we are making to the proposed provisions for consistency and clarity:

- We are making revisions to make the section consistent with the definition of "reprocessing" in final § 111.3, which refers only to "components or dietary supplements that have been previously removed from manufacturing."
- We are adding "treatments" as a step that quality control personnel could approve, because that term better describes actions that could be taken to correct a deviation or unanticipated occurrence with a component, packaging, or label.
- We are clarifying that it is quality control personnel who reject components, packaging, or labels.
- We are clarifying that quality control personnel approve the treatment, in-process adjustment, or reprocessing rather than determine whether the treatment, in-process adjustment, or reprocessing is possible.
- We are clarifying that, with respect to labels, the provision applies to the potential that a label not specified in the master manufacturing record could be used.
- We are making changes to be consistent with the new provision, final § 111.77.

(Comment 205) One comment recommends deletion of proposed § 111.35(i)(4) and (i)(4)(i), arguing that the principles of those sections are covered under proposed § 111.35(i)(2) and (i)(3).

(Response) We disagree with the comment's assertion. The requirements of proposed § 111.35(i)(4) and (i)(4)(i) are not covered by proposed

§ 111.35(i)(2) and (i)(3). All the sections are related, but deal with different aspects of corrective action. Proposed § 111.35(i)(2) and (i)(3) would require the firm to conduct a material review and make a disposition decision, while proposed § 111.35(i)(4) would prohibit the use of rejected ingredients unless the quality control unit determines that in-process adjustments are possible to correct the deviations or occurrence. We are making no changes as suggested by this comment and the primary elements of proposed § 111.35(i)(4) are retained in final § 111.90.

(Comment 206) A few comments state their support for the requirement that the quality control unit have the authority to determine whether adjustments are possible to correct a deviation.

(Response) We are retaining the proposed requirement for quality control personnel in final § 111.90.

2. Final § 111.90(a)

Final § 111.90(a) requires that you must 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: (1) Quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment and (2) the reprocessing, treatment, or in-process adjustment is permitted by § 111.77.

Final § 111.90(a) derives from proposed §§ 111.35(i)(4)(ii) and 111.50(d)(1). We revised this provision to be consistent with the changes in final § 111.77.

(Comment 207) Several comments state their support for proposed § 111.35(i)(4)(ii), which would require the quality control unit to approve the reprocessing of any rejected component, dietary ingredient, or dietary

supplement. However, not all comments agree that the quality control unit should have to conduct (under proposed § 111.50(d)(1)), rather than review and approve, a material review and disposition decision.

(Response) As discussed in this section, by "conduct a material review and make a disposition decision," we do not intend to limit those who may participate in a material review and disposition decision to only those persons acting in their capacity as designated quality control personnel. Others may assist quality control personnel in gathering and considering information relevant to the review and decision, however the quality control personnel have the responsibility to conduct a material review and make disposition decisions. Thus, we are retaining in final § 111.90(a) the requirements in proposed §§ 111.25(i)(4)(ii) and 111.50(d)(1).

3. Final § 111.90(b)

Final § 111.90(b) requires that you must 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: (1) Quality control personnel conduct a material review and make a disposition decision based on a scientifically valid reason and approve the reprocessing, treatment, or in-process adjustment and (2) the reprocessing, treatment or in-process adjustment is permitted by § 111.77. Final § 111.90(b) derives from proposed §§ 111.35(i)(4)(iii), 111.50(f), and 111.65(d). We revised this provision to be consistent with the changes in final § 111.77.

(Comment 208) As discussed in section VI of this document (discussion of the definition of "reprocessing"), some comments object to the restrictions in the definition of reprocessing in proposed § 111.3 because the definition would not permit the reprocessing of ingredients that may have been removed

because of insanitary conditions even if there are processes available that are safe and effective in removing foreign matter, microorganisms, or chemicals that may have rendered the ingredient "insanitary." These comments also object to proposed § 111.35(i)(4)(iii) for the same reasons. A few comments argue that a manufacturer should be able to reprocess a component or dietary supplement if it has been rejected because of contamination with microorganisms or types of contamination, such as heavy metals, if the quality control unit approves the reprocessing. These comments indicate this is the industry practice, one based on a scientific rationale for doing the reprocessing and that ensures other quality attributes of the product are not affected.

Some comments state that the requirement is more strict than the food or drug CGMP requirements, noting that reprocessing is widely accepted and allowed in the food CGMPs. Other comments believe that the prohibition in proposed § 111.35(i)(4)(iii) against reprocessing materials contaminated with microorganisms should be limited to materials contaminated with health-hazardous microorganisms.

(Response) As we discussed in the response to comment 53 for the definition of "reprocessing," we agree with the comments that state that in-process materials can be reprocessed when there are suitable processes available. However, as noted by the comments, it is critical that there be appropriate oversight of the reprocessing so the quality of the dietary supplement is not compromised. Final § 111.90(b) provides for the flexibility requested by the comments, provided that there is oversight by quality control personnel.

(Comment 209) Proposed § 111.35(i)(4)(iii) mentions "microorganism or other contaminants, such as heavy metals." One comment proposes that other

contaminants, such as pesticides and aflatoxin, should be mentioned. Another comment suggests that the final rule should specify limits for heavy metals in dietary supplements.

(Response) We decline to revise the final rule as suggested by the comments. It is impractical to provide an exhaustive list of relevant types of contamination, and a list that is longer, but not exhaustive, is more likely to be misunderstood as suggesting that the only types of contamination that are significant are the types of contamination in the list. For that reason, we have eliminated the reference to contamination to clarify that in any instance where it is appropriate quality control personnel must ensure that the disposition decision is based on a scientifically valid reason and also approve the reprocessing.

(Comment 210) One comment notes that in the May 9, 2003, satellite broadcast concerning the 2003 CGMP Proposal, we indicated that treating a component or dietary supplement with irradiation as a means to reduce or eliminate the microbial load was acceptable as long as the treatment was part of the process for producing that material. The comment asks for confirmation that irradiation of components or dietary supplements is allowed under part 179 (21 CFR part 179), even though such treatments are not listed in the table provided in § 179.26(b).

(Response) We are unable to provide the requested confirmation. Under section 201(s) of the act, irradiation intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food is a food additive that requires premarket review and approval before it can be used in food. Our Office of Food Additive Safety is currently reviewing a food additive petition for the use of irradiation on

dietary ingredients and dietary supplements. Until that review process is completed and we have authorized this use of irradiation through a final rule codified in part 179, irradiation of dietary ingredients and dietary supplements as a means to reduce or eliminate microbial loads is not permitted. However, you may use an irradiated component (such as a spice that is used to flavor a dietary supplement) when the irradiation of that component is allowed under § 179.26.

4. Final § 111.90(c)

Final § 111.90(c) requires that 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 be approved by quality control personnel and comply with final § 111.123(b) before releasing for distribution. Final § 111.90(c) derives from proposed § 111.50(g).

Final § 111.90(c) also includes conforming revisions to clarify that a dietary supplement that contains a component treated before use or adjusted in-process, or that has had in-process adjustments to make it suitable for use in the manufacture of a dietary supplement, must be approved by quality control personnel and comply with final § 111.123(b) before releasing for distribution. We revised this provision to be consistent with the changes in final §§ 111.77 and 111.123(b).

Final § 111.90(c) also includes revisions to reflect the final provisions that relate to reprocessing and in-process adjustments (see final §§ 111.113, 111.120, and 111.155).

(Comment 211) One comment asserts that a reprocessed product should be retested to confirm that it meets product specifications.

(Response) Under final § 111.75(c) and (d) quality control personnel have flexibility to determine whether tests or examinations are necessary to ensure that a reprocessed product meets product specifications.

*P. Under This Subpart, What Records Must You Make and Keep? (Final § 111.95)*

1. Final § 111.95(a)

Final § 111.95(a) requires you to make and keep records required under this subpart in accordance with subpart P. Final § 111.95(a) derives from proposed § 111.35(o). Some of the records required under subpart E are set forth as recordkeeping requirements in other subparts of this final rule, such as those related to receiving records for components, packaging, and labels in subpart G, and the results of testing or examination in subpart J. The record requirements not specifically required in other related subparts are listed in subpart E.

(Comment 212) One comment supports the recordkeeping requirements, states that the records provide a valuable paper trail that will allow manufacturers to identify and fix problems in the process, and suggests the requirements protect consumers from adulterated and misbranded products.

(Response) We agree. Under final § 111.95(a), a firm must make and keep records required by subpart E in accordance with subpart P. As discussed in this section, firms are required to keep the records necessary for determining whether their products are made in accordance with specifications. This will help them identify and correct any problems. In addition, under subpart P, the records must be kept for 1 year past the shelf life date (if shelf life dating is used) or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. Moreover, firms must make their

records available to us for inspection and copying, which will permit us to determine whether firms are manufacturing, packaging, labeling, and holding dietary supplements in accordance with the requirements of this rule.

2. Final § 111.95(b)

Final § 111.95(b) specifies the records you must make and keep under subpart E. Under the reorganization several recordkeeping requirements of proposed § 111.35 are set forth in other subparts.

Final § 111.95(b)(1) requires you to make and keep records of the specifications established. Final § 111.95(b)(1) derives from proposed § 111.35(o)(1).

Final § 111.95(b)(2) requires you to make and keep records of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis. Final § 111.95(b)(2) is a record that is required under final § 111.75(a)(2)(B).

Final § 111.95(b)(3) requires you to make and keep 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. Final § 111.95(b)(3) refers to records required under final § 111.70(c)(2).

Final § 111.95(b)(4) requires you to make and keep documentation for why the results of appropriate tests or examinations for the product specifications selected under final § 111.75(c)(1) ensures that the dietary supplement meets all product specifications. Final § 111.95(b)(4) is a record that is required under final § 111.75(c)(3).

Final § 111.95(b)(5) requires you to make and keep 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 final § 111.75(d) is met without verification through periodic testing of the finished batch, including documentation that the selected specifications tested or examined under final § 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. Final § 111.95(b)(5) refers to a record required under final § 111.75(d)(1). As previously discussed in this section, we are issuing an interim final rule, published elsewhere in this issue of the **Federal Register**, that sets forth a procedure for requesting an exemption from the requirement that the manufacturer conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient. Included in the interim final rule is an amendment to final § 111.95(b) adding a new paragraph (b)(6) requiring the retention of FDA's response to a petition submitted under § 111.75(a)(1)(ii) that provides for an exemption from the provision of § 111.75(a)(1)(i).

(Comment 213) One comment recommends the recordkeeping requirements of proposed § 111.35(m) be moved to follow the requirements for appropriate test methods because these requirements are related and probably best understood without intervening information.

(Response) Consistent with this comment, the recordkeeping requirements of proposed § 111.35(m) are set forth in final subpart J instead of subpart E.

## XI. Comments on Requirements for Quality Control (Final Subpart F)

### *A. Organization of Final Subpart F*

Proposed § 111.37 set forth requirements for quality control operations. Other proposed requirements related to quality control operations were set forth in other sections. For example, proposed § 111.40(a) would require the quality control unit to perform operations associated with components that you use in the manufacturing process. Proposed § 111.45 would establish requirements for the master manufacturing record and would have the quality control unit review and approve each master manufacturing record. Proposed § 111.50 would have the quality control unit review batch production records.

As shown in table 7 of this document, the final rule reorganizes the requirements related to quality control operations into a distinct subpart (final Subpart F—Production and Process Control System: Requirements for Quality Control Operations). Table 7 lists the sections in final subpart F and identifies the proposed sections that form the basis for the sections in the final rule.

TABLE 7.—DERIVATION OF SECTIONS IN FINAL SUBPART F

| Final Rule | 2003 CGMP Proposal |
|---|---|
| § 111.103 What are the requirements under this subpart F for written procedures? | N/A |
| § 111.105 What must quality control personnel do? | § 111.37(a), (b)(1), (b)(11), and (b)(12) |
| § 111.110 What quality control operations are required for laboratory operations associated with the production and process control system? | § 111.37(b)(9) and (b)(13) |
| § 111.113 What quality control operations are required for a material review and disposition decision? | § 111.35(i)(2), (i)(3), (i)(4)(i), (i)(4)(ii), (j), and (n)<br>§ 111.37(b)(3)<br>§ 111.37(c)<br>§ 111.40(a)(3) and (b)(2)<br>§ 111.50(d)(1)<br>§ 111.65(d)<br>§ 111.70(c) |

TABLE 7.—DERIVATION OF SECTIONS IN FINAL SUBPART F—Continued

| Final Rule | 2003 CGMP Proposal |
|---|---|
| § 111.117 What quality control operations are required for equipment, instruments, and controls? | § 111.30(b)(4), (b)(6), (b)(7), and (b)(8) |
| § 111.120 What quality control operations are required for components, packaging, and labels before use in the manufacture of a dietary supplement? | § 111.35(i)(4)(i) and (i)(4)(ii)<br>§ 111.37(b)(2) and (b)(10)<br>§ 111.40(a)(3) and (b)(2)<br>§ 111.50(e)(1) |
| § 111.123 What quality control operations are required for the master manufacturing record, the batch production record, and manufacturing operations? | § 111.35(e)(2), (f), (i)(2), and (o)(2)<br>§ 111.37(b)(2), (b)(4), (b)(5), and (b)(11)(iii)<br>§ 111.45(c)<br>§ 111.50(d)(1) and (d)(2)<br>§ 111.50(g) |
| § 111.127 What quality control operations are required for packaging and labeling operations? | § 111.37(b)(2) and (b)(10)<br>§ 111.40(a)(2) and (a)(3)<br>§ 111.70(c), (d), and (e) |
| § 111.130 What quality control operations are required for returned dietary supplements? | § 111.37(b)(2) and (b)(15)<br>§ 111.85(a) |
| § 111.135 What quality control operations are required for product complaints? | § 111.95 |
| § 111.140 Under this subpart F, what records must you make and keep? | § 111.35(j)<br>§ 111.37(c) and (d) |

*B. Highlights of Changes to the Proposed Requirements for Quality Control Operations*

1. Revisions

The final rule:

- Reflects that the rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion under § 111.1;
- Changes the requirement for a quality control unit to a requirement for quality control operations performed by quality control personnel;
- Requires quality control personnel to review and approve documentation for why meeting in-process specifications will ensure the

specifications for identity, purity, strength, and composition of a dietary supplement are met;

- Requires quality control personnel to review and approve documentation setting forth the basis for qualifying a supplier of a component;
- Requires quality control personnel to review and approve documentation of your basis for why meeting certain selected specifications in a subset of finished batches will ensure your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, and composition and limits on those types of contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and
- Requires quality control personnel to review and approve documentation for why a product specification exempted from the verification requirements in final subpart E is met without verification through periodic testing of the finished batch.

2. Changes Associated With the Reorganization

The final rule:

- Reduces redundant provisions and
- Combines parts of various proposed requirements that were scattered throughout the 2003 CGMP Proposal.

3. Changes After Considering Comments

The final rule:

- Incorporates a new requirement to establish, and keep as a record, written procedures for quality control operations;
- Simplifies the requirements associated with conducting a material review and making a disposition decision;

- Requires quality control personnel to ensure that representative samples are collected rather than collecting these samples;
- Requires quality control personnel to ensure that reserve samples are held rather than quality control personnel holding these samples;
- Requires quality control personnel to ensure tests or examinations are appropriate rather than conduct these tests or examinations; and
- Requires review by quality control personnel of all records for calibration of instruments, and for calibrations, inspections, and checks of automatic, mechanical, or electronic equipment to be performed on a periodic basis rather than at the time the record is made.

*C. General Comments on Proposed § 111.37 (Final Subpart F)*

(Comment 214) Some comments support the use of a quality control unit and recognize it as an important need in manufacturing operations. Some comments assert the quality control unit may not have all the responsibilities listed in proposed § 111.37 because there may be some duties contracted out to someone else, such as testing that could be sent to a contract laboratory, or some duties that may be better suited for employees in other organizational units. As an example, a few comments note that the instrument and equipment calibration functions in proposed § 111.37 may be better performed by individuals responsible for the equipment in their particular operational area, by those in a unit dedicated to equipment maintenance and calibration, or possibly by a third party, who is qualified by training and/or experience, to do these functions. Similarly, other comments note that other groups with the appropriate expertise may be assigned or required to review and approve proposed changes or procedures in manufacturing operations or to conduct material reviews and make disposition decisions. These comments assert the

quality control unit should have overall responsibility and oversight for quality control functions but also should be able to rely on the expertise of other persons in the organization to accomplish the tasks.

(Response) As already discussed with respect to the definition of quality control personnel in section VI of this document, these comments may have misunderstood the quality control unit's role under the proposed rule. Consequently, we have added final § 111.12(b) in subpart B, discussed in section VII of this document, to state you must identify who is responsible for your quality control operations. Each person who is designated to perform quality control operations must be qualified to do so and have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

The final rule requires quality control personnel to ensure all appropriate tests and examinations are conducted, and review and approve the results of all tests and examinations, but does not require that quality control personnel conduct the tests or examinations. Thus, you would not need to consider that an individual who conducts tests or examinations at a laboratory under contract to your organization is performing a quality control operation that must be performed by quality control personnel. However, you may choose to designate that individual as part of your quality control personnel and require that the tests or examinations conducted by that individual be quality control operations. Importantly, however, for the purposes of this final rule, we consider that a quality control operation performed by an individual under contract to you or by another third party is no different than a quality control operation performed by your employees who are designated to perform such

operation. If, during the course of an inspection, we find the requirements of this final rule were not followed, we will hold you, rather than the contractor or other third party, responsible. The applicability of this final rule to contractors is discussed in detail in section VI of this document.

(Comment 215) Several comments request that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) We agree with these comments and have revised several provisions accordingly. For example, in the 2003 CGMP Proposal we would require the quality control unit to perform appropriate tests and examinations of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements (proposed § 111.37(b)(13)). Under the final rule, quality control operations include ensuring appropriate tests and examinations are conducted (final § 111.110(b)) but do not include conducting these tests and examinations.

(Comment 216) One comment asks whether we expect the quality control unit to approve operational activities as soon as they occur or collectively at the end of the process. This and other comments argue the quality control function is usually accomplished by a team of qualified persons with the quality control unit having the overall responsibility and authority to perform a collective, post-processing, final approval.

(Response) The time at which quality control personnel conduct assigned duties will vary by the specific operation, the size and complexity of the operation, and how quality control functions are assigned to qualified persons. For example, the final rule requires quality control personnel to determine whether components conform to specifications, and to release components

from quarantine before you use them in the manufacture of a dietary supplement (final § 111.120). However, this final rule does not require, for example, that quality control personnel determine whether components conform to specifications as soon as you receive them, although it may be common business practice to do so.

Regardless of when quality control personnel perform their operations, quality control personnel have the ultimate responsibility for ensuring manufacturing, packaging, labeling, and holding operations are performed in a manner that will ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

*D. What Are the Requirements Under This Subpart for Written Procedures? (Final § 111.103)*

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

Final § 111.103 requires that you establish and follow written procedures for the responsibilities of the quality control operations. Final § 111.103 specifically identifies two of the written procedures you must establish and follow, i.e., written procedures for conducting a material review and making a disposition decision and for approving or rejecting any reprocessing.

*E. What Must Quality Control Personnel Do? (Final § 111.105)*

Final § 111.105 broadly captures the responsibility of quality control personnel to provide oversight for manufacturing, packaging, labeling, and holding operations. It 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. Final § 111.105 derives from proposed § 111.37(a) which would require you to use a quality control unit to ensure your manufacturing, packaging, labeling, and holding operations in the production of dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring dietary supplements meet specifications for identity, purity, quality, strength, and composition.

This final rule focuses on ensuring that the manufacturer establishes specifications for its dietary supplements; includes those specifications in the master manufacturing record; meets those specifications and manufactures, packages, labels, and holds the product in a manner that will ensure the quality of the dietary supplement; and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Because of that focus, the labeling requirements of the final rule address the operation of putting the label that is specified in the master manufacturing record on the product rather than the content of a product label that meets all of the labeling requirements of the act and our implementing regulations. The failure to put the label identified in the master manufacturing record on the finished product would be a violation of this final rule. In addition, if the label on the product does not correctly reflect the ingredients, the label would misbrand the product under section 403 of the act. For purposes of this final rule, the labeling operations are CGMP requirements and relate to the label identified in the master manufacturing record. Therefore, we are deleting "misbranding" from proposed § 111.37(a) (final § 111.105) since the act of misbranding other than

applying a label different from the one identified in the master manufacturing record is not considered a CGMP violation in the context of this final rule. Any misbranding is still a violation of the act, however, and manufacturers must comply with all applicable statutory and regulatory requirements in addition to the requirements of this final rule.

This series of changes emphasizes the need to ensure the quality of a dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. As discussed in detail in the rest of this section, final § 111.105 also requires that quality control personnel perform certain operations and groups of operations.

1. Final § 111.105(a)

Final § 111.105(a) requires that quality control personnel approve or reject 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. Final § 111.105(a) derives from proposed § 111.37(b)(1).

(Comment 217) One comment recommends revising proposed § 111.37(b)(1) by replacing "* * * identity, purity, quality, strength, and composition" with "* * * identity, purity, quality, strength, or composition." The comment asserts the quality control unit must be responsible for approving or rejecting anything that may affect one of these attributes.

(Response) We agree with this comment. Under proposed § 111.37(b)(1) we had intended that the quality control unit be responsible, for example, for approving a test that would establish the identity of a component even if that test did not also establish the strength of that component. Final § 111.105(a) changes "and" to "or" as requested by this comment.

(Comment 218) One comment recommends the quality control unit be responsible for maintaining the master copies of all current and approved written procedures, for distributing copies of approved written procedures to relevant personnel, and for collecting and destroying outdated Standard Operating Procedures (SOPs) (except designated historical SOP files).

(Response) This comment is consistent with the underlying principle that quality control personnel oversee the design and conduct of the operations associated with the production of a dietary supplement. After considering these comments, final § 111.105(a) requires quality control personnel to approve all written procedures that may affect the identity, purity, strength, or composition of a dietary supplement. With respect to the other suggested duties of quality control personnel, we are leaving the decision as to who performs them, up to the individual firm to best suit its overall operations.

2. Final § 111.105(b), (c), d), and (e)

Final § 111.105(b) requires quality control personnel to review and approve the documentation setting forth the basis for qualification of any supplier. Final § 111.105(c) requires quality control personnel to review and approve the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that specifications for the identity, purity, strength, and composition of the dietary supplement are met. Final § 111.105(d) requires quality control personnel to review and approve the documentation setting forth the basis for why the results of appropriate tests or examinations for each product specification selected under final § 111.75(c)(1) will ensure that the finished batch of the dietary supplement meets product specifications. Final § 111.105(e) requires quality control personnel to review and approve the basis

and documentation for why any product specification is exempted from the verification requirements in final § 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.

Final § 111.105(b), (c), (d), and (e) are requirements associated with the requirements established in final §§ 111.70(c)(3) and 111.75(a)(ii)(2)(E), (c)(4), (d)(1) and (d)(2).

3. Final § 111.105(f)

Final § 111.105(f) requires quality control personnel to ensure that required representative samples are collected. Final § 111.105(f) differs slightly from proposed § 111.37(b)(11)(i) through (b)(11)(iv) which would require the quality control unit to collect representative samples of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements.

After considering comments requesting the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks themselves, the final rule does not specify that quality control personnel must collect representative samples. Under final § 111.105(f), however, quality control personnel retain oversight of sample collection.

4. Final § 111.105(g)

Final § 111.105(g) requires quality control personnel to ensure that required reserve samples are collected and held. Final § 111.105(g) derives from proposed § 111.37(b)(12) which would require the quality control unit to keep reserve samples.

After considering comments requesting the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks themselves, the final rule does not specify that quality control personnel must keep reserve samples. Under final § 111.105(g), however, quality control personnel retain oversight of sample collection and holding.

5. Final § 111.105(h)

Final § 111.105(h) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether all specifications established in accordance with final § 111.70(a) are met. Final § 111.105(h) derives from proposed § 111.37(b)(2) which would require that the quality control unit determine whether all components, dietary supplements, packaging, and labels conform to specifications. Under the final rule, we are identifying each of the specifications subject to review by quality control personnel under final § 111.77. The requirement for quality control personnel to determine whether specifications established under final § 111.70(a) are met is included for consistency. This requirement is also consistent with final § 111.73 which requires that the production and process control system must include a determination of whether all of the established specifications under final § 111.70(a) are met.

6. Final § 111.105(i)

Final § 111.105(i) requires quality control personnel to perform other operations required under subpart F. Final § 111.105(i) is associated with the reorganization. Under the 2003 CGMP Proposal, proposed § 111.37(a) broadly captured the responsibility of the quality control unit to provide oversight for your manufacturing, packaging, labeling, and holding operations. Proposed

§ 111.37(b) listed specific operations that we would require the quality control unit to perform. Final § 111.105 now captures the responsibility of quality control personnel to provide oversight for your manufacturing, packaging, labeling, and holding operations. The specific operations that quality control personnel must perform to provide that oversight are set forth in final § 111.105(a) through (h) and in final §§ 111.110, 111.113, 111.117, 111.120, 111.123, 111.127, 111.130, 111.135, and 111.140.

*F. What Quality Control Operations Are Required for Laboratory Operations Associated With the Production and Process Control System? (Final § 111.110)*

Final § 111.110 sets forth the minimum required operations that quality control personnel must perform with respect to laboratory operations associated with the production and process control system.

1. Final § 111.110(a)

Final § 111.110(a) requires that quality control operations for laboratory operations include reviewing and approving all laboratory control processes associated with the production and process control system. Final § 111.110(a) derives, in part, from proposed § 111.37(b)(9) which would require that the quality control unit review and approve all laboratory control processes. For clarity, we are adding that the laboratory operations covered by final § 111.110 are those associated with the production and process control system. We want to make clear that laboratory operations such as those in your research and development department are not subject to final § 111.110.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(9).

2. Final § 111.110(b)

Final § 111.110(b) requires that quality control operations for laboratory operations associated with the production and process control system include ensuring all tests and examinations required under final § 111.75 are conducted. Final § 111.110(b) derives, in part, from proposed § 111.37(b)(13) which would require the quality control unit to perform appropriate tests and examinations of incoming materials, in-process materials, each finished batch of dietary supplements, and each batch of packaged and labeled dietary supplements.

Proposed § 111.37(b)(13) would list the types of materials that must be tested, including components, packaging, labels, dietary ingredients, and dietary supplements that you receive; the batch production at the in-process and finished batch stages; and packaged and labeled dietary supplements. This list would include materials that, at a minimum, would be tested under the 2003 CGMP Proposal. Under the final rule, the minimum requirements for testing or examination of the materials listed in proposed § 111.37(b)(13) are set forth in final § 111.75. To simplify and clarify proposed § 111.37(b)(13), final § 111.110(b) replaces this list with "all tests and examinations required under § 111.75."

3. Final § 111.110(c)

Final § 111.110(c) requires that quality control operations for laboratory operations associated with the production and process control system include reviewing and approving the results of all tests and examinations required under final § 111.75. Final § 111.110(c) derives from proposed § 111.37(b)(9), which would require, in part, that the quality control unit review and approve all testing results. Final § 111.110(c) requires that quality control personnel

review and approve the results of examinations as well as tests. This revision reflects the flexibility provided in the final rule to use either tests or examinations to determine whether specifications are met, provided that the test or examination is an appropriate, scientifically valid method.

As with final § 111.110(b), we provide in final § 111.110(c) that the tests and examinations are those required under final § 111.75.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(9).

*G. What Quality Control Operations Are Required for a Material Review and Disposition Decision? (Final § 111.113)*

Final § 111.113 derives from several proposed provisions, including §§ 111.35(i), (j), and (n); 111.37(b)(3); 111.40(a)(3) and (b)(2); 111.50(d)(1); 111.65(d); and 111.70(c). All these proposed requirements are related to one or more aspects associated with a material review and disposition, including the circumstances that require a material review and disposition decision, the documentation that must be included in a material review and disposition decision, any restrictions on who must conduct the material review and make the disposition decision, and the need for oversight by the quality control unit. As discussed in section X of this document, we simplified the provisions regarding a material review and disposition decision (final § 111.87), emphasizing the importance of oversight by quality control personnel and retaining the principle that qualified individuals other than those who are designated quality control personnel can contribute to the material review and disposition decision. The final rule sets forth the following requirements for quality control personnel that relate to final § 111.113:

- Under final § 111.87, quality control personnel must conduct all required material reviews and make all required disposition decisions;
- Under final § 111.103, you must establish and follow written procedures for conducting a material review and making a disposition decision; and
- Under final § 111.140(b)(3)(vii), documentation of a material review and disposition decision and followup must include the signature of the individual, designated to perform the quality control operation, who conducted the material review and made the disposition decision and of any qualified individual who provided information relevant to that material review and disposition decision.

The final rule establishes a system in which you have the flexibility to develop procedures that suit your organization, including having qualified individuals, who are not designated to perform the quality control operation, provide information relevant to the material review and disposition decision. For example, under final § 111.140(b)(3), you could have a qualified individual in the production department assist quality control personnel in conducting a material review by preparing a report that includes all the required documentation and information and providing a signed copy of that report to quality control personnel. An individual who is designated to perform the quality control operation could then use that report as part of the material review, conduct any further investigations, as necessary, and decide to accept, amend, or reject the report.

1. Final § 111.113(a)

Under final § 111.113(a) quality control personnel must conduct a material review and make a disposition decision if:

- A specification established in accordance with § 111.70 is not met;

- 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;
- 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;
- 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; or
- A dietary supplement is returned.

Final § 111.113(a) is substantially similar to proposed § 111.35(i)(3), which would require, in part, that you make a material disposition decision for any component, dietary supplement, packaging, or label:

- If a component, dietary supplement, packaging, or label fails to meet established specifications;
- If any step established in the master manufacturing record is not completed;
- If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary supplement, packaging, or label;
- If calibration of an instrument or control suggests a problem that may have caused batches of a dietary supplement to become adulterated; or
- If a dietary supplement is returned.

Final § 111.113(a) also incorporates elements from other proposed sections regarding the circumstances that require a material review and disposition decision as follows:

- Proposed § 111.35(n), which would require you, for any specification that is not met, to conduct a material review and disposition decision under proposed § 111.35(i);
- Proposed § 111.40(a)(3), which would require you, for components, dietary ingredients, or dietary supplements you receive, to conduct a material review and make a disposition decision if specifications are not met;
- Proposed § 111.40(b)(2), which would require that for packaging and labels you receive, you must conduct a material review and make a disposition decision if specifications are not met;
- Proposed § 111.50(d)(1), which would require that if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record;
- Proposed § 111.65(d), which would require you to conduct a material review and make a disposition decision in accordance with proposed § 111.35(i) for any component, dietary ingredient, or dietary supplement that fails to meet specifications or that is or may be adulterated; and
- Proposed § 111.70(c), which would require you to conduct a material review and make a disposition decision of any packaged and labeled dietary supplements that do not meet specifications.

In final § 111.113(a) we are incorporating, into a single unified provision, the various proposed circumstances that would require a material review and disposition decision under the 2003 CGMP Proposal. We included revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition

decision. We also included revisions associated with final § 111.90 that relate to the impact on labeling operations due to deviations and unanticipated occurrences.

In establishing final § 111.113(a)(1), we are deleting the specific reference to the articles (components, dietary supplements, packaging, and labels) required to undergo a material review. We are deleting these references, in part, to simplify the provision. Under final § 111.113(a) quality control personnel must conduct a material review and make a disposition decision if any specification established in accordance with final § 111.70 is not met. It is not necessary to repeat, in final § 111.113, the list of specifications that is clearly set forth in final § 111.70.

We did not receive comments specific to quality control operations under proposed §§ 111.35(i)(3) and (n), 111.40(a)(3) and (b)(2), 111.50(d)(1), 111.65(d), or 111.70(c).

2. Final § 111.113(b)

Final § 111.113(b)(1) requires that, 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, quality control personnel must reject the component, dietary supplement, or packaging, or label unless it approves a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence.

Final § 111.113(b)(1) derives from the following proposed provisions:

- Proposed § 111.35(i)(4)(i) which, in part, would require that, for any deviation or unanticipated occurrence which resulted in or could lead to

adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, you reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence;

- Proposed § 111.35(i)(4)(ii) which, in part, would require that, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, you not reprocess a rejected component or dietary supplement unless approved by the quality control unit; and

- Proposed § 111.37(b)(3) which, in part, would require the quality control unit to approve or reject all dietary ingredients, dietary supplements, components, packaging, and labels.

For consistency with other provisions in final subpart F, final § 111.113(b)(1) requires that quality control personnel "reject" a component, dietary supplement, packaging, or label. We also included revisions that are associated with final § 111.90.

Final § 111.113(b)(2) requires that when a specification established in accordance with § 111.70 is not met, quality control personnel must reject the component, dietary supplement, package, or label, unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in final § 111.77. This provision has been added as a result of the new provision, final § 111.77 which provides for what happens when certain specifications are not met, the responsibilities of quality control personnel, and the changes made to final § 111.90.

(Comment 219) Several comments request that the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) We agree, and final § 111.113(b) provides that quality control personnel "approve" an in-process adjustment rather than "determine whether" the in-process adjustment is possible.

3. Final § 111.113(c)

Final § 111.113(c) requires the person who conducts a material review and makes the disposition decision, at the time of performance, to document that material review and disposition decision. Final § 111.113(c) derives from proposed § 111.35(j) which, in part, would require that the person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in proposed § 111.35(i).

As an editorial revision, final § 111.113(c) requires documentation of "that" decision rather than "every" decision. As a practical matter, under final § 111.113(c) every material review and disposition decision is documented.

We did not receive comments specific to quality control operations under proposed § 111.35(j).

*H. What Quality Control Operations Are Required for Equipment, Instruments, and Controls? (Final § 111.117)*

Final § 111.117 (proposed § 111.37(b)(6) through (b)(8)) sets forth the minimum required operations that quality control personnel must perform with respect to equipment, instruments, and controls.

1. Final § 111.117(a) through (c)

Final § 111.117(a) through (c) requires the quality control operations for equipment, instruments, and controls to include:

- Reviewing and approving all processes for calibrating instruments and controls;
- Periodically reviewing all records for calibration of instruments and controls; and
- Periodically reviewing all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment.

Final § 111.117(a), (b), and (c) derive from proposed § 111.37(b)(6), (b)(7), and (b)(8) which would require the quality control unit to:

- Review and approve all processes for calibrating instruments or controls;
- Review all records for calibration of instruments, apparatus, gauges, and recording devices; and
- Review all records for equipment calibrations, inspections, and checks.

Final § 111.117 includes the following changes we are making for consistency with the requirements, set forth in subpart D, for equipment and utensils:

- We have deleted the terms "apparatus," "gauges," and "recording devices" from proposed § 111.37(b)(7) as they would fall under the terms "instruments and controls" in final § 111.117, and because subpart D does not use the terms "apparatus," "gauges," or "recording devices."
- We are characterizing the records for equipment calibrations, inspections, and checks as records for calibrations, inspections, and checks of "automated, mechanical, or electronic equipment," because final § 111.30(c) requires you to calibrate, inspect, or check "automated, mechanical, or electronic equipment."

(Comment 220) One comment argues the requirements for oversight by the quality control unit in proposed § 111.37(b)(7) and (b)(8) are excessive and go beyond requirements for both the drug CGMPs and food CGMPs. The comment recommends revising proposed § 111.37(b)(7) and (b)(8) to require a review of all records when there is a negative impact on the product due to a calibration failure.

Other comments refer to the related requirements in proposed § 111.30(b)(1) that the quality control unit approve calibrations, inspections, or checks of automatic, mechanical, or electronic equipment. These comments assert the requirement for the quality control unit to approve such calibrations, inspections, and checks of equipment is too prescriptive and that qualified persons outside of the quality control unit should be able to approve these calibrations, inspections, or checks. These comments also assert the quality control unit should perform audits of the records generated to ensure the appropriate calibrations, inspections, and checks are being adequately performed at the required intervals.

(Response) As already discussed with respect to proposed § 111.30(b)(1) (final § 111.30(c)), we disagree that the review by quality control personnel should be limited to circumstances when there has been a calibration failure. One of the oversight functions of quality control personnel is to prevent problems with the product you distribute by finding any problems with the equipment you use to produce the product rather than to investigate the cause of a problem with a product that you already distributed. However, we agree it is sufficient to review the records of calibrations, inspections, and checks of automated, mechanical, or electronic equipment periodically, for example, on an annual basis, rather than to approve each record when it is made. A

periodic review can uncover trends in the performance of the equipment that have the potential to adversely affect the quality of the dietary supplement and that may not be obvious by merely approving each record when it is made. Seeing such trends would enable quality control personnel to recommend actions to correct the trend. Therefore, we have revised the proposed requirement so that under final § 111.117(c) quality control personnel must review all records of calibrations, inspections, and checks of automatic, mechanical, or electronic equipment on a periodic basis. Likewise, we have revised the rule so that the quality control personnel's review of all records of equipment calibrations also is on a periodic basis.

(Comment 221) A few comments argue the review of calibration records may be conducted by a qualified person other than the quality control unit, such as by a supervisor or by a separate department dedicated to equipment maintenance and calibration. These comments assert the quality control unit should approve calibration processes, but review of completed calibration records by the dedicated department is sufficient to assure compliance with the approved process.

(Response) As already discussed, many comments about the quality control unit may have misunderstood the proposed definition of "quality control unit" (now replaced by "quality control personnel"). Under final § 111.12(b), you must 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 have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. Thus, in the situation described by these comments, you could identify a qualified person

in a department dedicated to equipment maintenance and calibration to perform quality control operations for equipment calibration. Neither the definition of "quality control personnel," nor the requirements of final § 111.12(b), would preclude a person who performs "Operation X" from being identified as the person who performs quality control operations for "Operation X." However, we strongly recommend that the person you identify to perform a given quality control operation be a different person than the person who performed the operation that is subject to quality control oversight.

2. Final § 111.117(d)

Final § 111.117(d) requires that quality control operations for equipment, instruments, and controls include reviewing and approving controls to ensure automated, mechanical, or electronic equipment functions in accordance with its intended use. Final § 111.117(d) derives, in part, from proposed § 111.30(b)(4) (final § 111.30(e)) which would require that, for any automated, mechanical, or electronic equipment you use, you must establish and use appropriate controls and the controls are approved by your quality control unit to ensure that the equipment functions in accordance with its intended use. We are clarifying the proposed requirement related to quality control personnel in final § 111.117(d).

We did not receive comments specific to this responsibility of the quality control unit in proposed § 111.30(b)(4).

*I. What Quality Control Operations Are Required for Components, Packaging, and Labels Before Use in the Manufacture of a Dietary Supplement? (Final § 111.120)*

Final § 111.120 sets forth the minimum required operations that quality control personnel must perform with respect to components, packaging, and

labels before use in the manufacture of a dietary supplement. Some of the proposed provisions that form the basis for final § 111.120 included requirements for "dietary supplements that you receive." For example, proposed § 111.40(a) would require you, for components or dietary supplements you receive, to visually examine containers and documentation provided by the supplier, quarantine the materials until they are released by the quality control unit, and identify the materials in a manner that allows you to trace the shipment you receive to the product that you manufacture and distribute. The final rule separates these and other requirements for quality control operations for "product that you receive from a supplier" for packaging or labeling as a dietary supplement from the analogous requirements for components. Thus, the requirements for quality control operations for product you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier) are found in final § 111.127 rather than final § 111.120.

1. Final § 111.120(a)

Final § 111.120(a) requires that quality control operations for components, packaging, and labels include reviewing all receiving records for components, packaging, and labels before use. Final § 111.120(a) derives from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records;

- Proposed § 111.40(a)(3) which, in part, would require that you quarantine dietary supplements until your quality control unit reviews the supplier's invoice, guarantee, or certification; and
- Proposed § 111.50(e)(1) which, in part, would require the quality control unit to document its review of component receiving records.

(Comment 222) One comment asserts that the proposed requirement that the review of the batch record by the quality control unit include cross-referencing of receiving records with the batch production record is redundant and should be mandatory only in cases where a specification has not been met. This comment asserts the quality control unit has already reviewed and approved components, packaging, and labels prior to their release and has used unique identifiers for these raw materials as they are recorded on related documentation and records, which allow traceability back to this documentation for review when necessary. This comment also asserts all material review and disposition decisions must be documented and these will include the unique identifiers that tie them to particular raw or in-process materials.

Another comment asserts that the quality control unit should only need to repeat a review of the receiving records as a result of conducting an investigation or a material review, as is required for drugs, and to require otherwise would be redundant. This comment also states requiring the quality control unit to repeat its review of the receiving records places a fairly large burden on the quality control unit because this re-review must be performed for each and every batch production record. The comments assert the requirement should be completed properly and only once.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12200), we stated that cross-referencing receiving and batch production records means the quality control unit must verify that the batch record includes certain documentation of the receiving records for the components such as the unique identifier assigned to the shipment lot of components, testing results, a material review and disposition decision, if conducted, and approval for use by the quality control unit. We agree with the comments that the review of records such as receiving records (including proper documentation of a unique identifier for components, packaging, and labels), if done properly the first time it is performed, need not be repeated. Therefore, the final rule does not include any requirement for cross-referencing receiving records with the batch production record as we would require under proposed § 111.37(b)(10). As noted, we have changed "quality control unit" to "quality control personnel." We agree that cross-referencing receiving and batch production records is an appropriate step to take when conducting a material review and making a disposition when, for example, a specification is not met. We encourage firms to include this activity in the written procedures for conducting a material review and making a disposition decision.

2. Final § 111.120(b)

Final § 111.120(b) requires that quality control operations for components, packaging, and labels include determining whether all components, packaging, and labels conform to specifications established under § 111.70(b) and (d) before use. Final § 111.120(b) derives from proposed § 111.37(b)(2).

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2). For clarity, we have identified the specifications as those required under final § 111.70(b) and (d).

3. Final § 111.120(c)

Final § 111.120(c) requires that quality control operations for components, packaging, and labels include conducting any required material review and making any required disposition decision before use. Final § 111.120(c) derives from the following proposed provisions:

- Proposed § 111.40(a)(3) which, in part, would require you to conduct a material review and make a disposition decision if specifications are not met for components; and
- Proposed § 111.40(b)(2) which, in part, would require you to conduct a material review and make a disposition decision if specifications are not met for packaging and labels.

Final § 111.120(c) includes revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition decision.

(Comment 223) One comment recommends the quality control unit have authority to allow usage of material that has failed to meet specifications if the defect will not significantly affect the overall quality of the finished product even if reprocessing is not an option. The comment gives an example of a material that fails to meet particle size specifications designed to maximize the efficiency of processing of the material, but ultimately does not impair strength, and asserts the quality unit should have the authority to release the material for use.

(Response) The final rule provides for a process in which quality control personnel determine whether a component meets specifications and conduct a material review and make a disposition decision if a component does not meet one or more specifications. The final rule does not prohibit the use of

a component that does not meet all component specifications other than the identity specification. For example, under final § 111.120(d) quality control personnel may approve an in-process adjustment of a component to make it suitable for use in the manufacture of a dietary supplement (see discussion of final § 111.120(d) in the following paragraphs). Under final § 111.123(b) quality control personnel must not approve and release for distribution any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications or is not a quality product. Thus, although a disposition decision could be made under final § 111.120(c) to use a component even if it does not meet certain specifications, that decision should take into account whether the failure for the component to meet specifications will ultimately cause the dietary supplement to fail to meet product specifications.

4. Final § 111.120(d)

Final § 111.120(d) requires that quality control operations for components, packaging, and labels include approving, or rejecting, any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement. Final § 111.120(d) derives from the following proposed provisions:

- Proposed § 111.35(i)(4)(i) which, in part, would require that you reject the component, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence and

- Proposed § 111.35(i)(4)(ii) which would have prohibited you from reprocessing a rejected component unless approved by the quality control unit.

Final § 111.120(d) includes a revision associated with final § 111.90(c), and refers to "treatment and in-process adjustments to make them suitable for use in the manufacture of a dietary supplement" (see discussion of final § 111.90(c) in section X of this document).

(Comment 224) Several comments request the quality control unit focus on reviewing tasks performed by others rather than on performing the tasks itself.

(Response) Final § 111.120(d) includes a revision that quality control personnel "approve" a treatment rather than "determine that" the treatment is possible.

(Comment 225) A few comments support the proposed requirement that the quality control unit have the authority to approve reprocessing measures.

(Response) These comments are consistent with proposed § 111.35(i) and (i)(4)(ii) and final § 111.120(d), as applicable to quality control personnel.

(Comment 226) One comment states that the decision to reprocess a material belongs within the particular operational unit, and that the role of the quality control unit should be to approve the results of the reprocessing.

(Response) We disagree that the role of quality control personnel should be limited to approving the results of reprocessing or, in this case, of the treatment or in-process adjustments of components, packaging, or labels. An underlying principle of these CGMP requirements is that quality control personnel oversee the design and conduct of manufacturing, packaging, labeling, and holding operations. A decision about when reprocessing is, or is not, appropriate requires oversight.

As already discussed, under final § 111.12(b) you must 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 have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

5. Final § 111.120(e)

Final § 111.120(e) requires that quality control operations for components, packaging, and labels include approving and releasing from quarantine all components, packaging, and labels before they are used. Final § 111.120(e) derives from the following proposed provisions:

- Proposed § 111.40(a)(3) which, in part, would require that you quarantine components until your quality control unit approves the components and releases them from quarantine and
- Proposed § 111.40(b)(2) which, in part, would require that you quarantine packaging and labels until your quality control unit approves the packaging and labels and releases them from quarantine.

We did not receive comments specific to quality control operations under proposed § 111.40(a)(3) or (b)(2).

*J. What Quality Control Operations Are Required for the Master Manufacturing Record, the Batch Production Record, and Manufacturing Operations? (Final § 111.123)*

Final § 111.123 sets forth the minimum required operations that quality control personnel must perform with respect to the master manufacturing record, the batch production record, and manufacturing operations.

1. Final § 111.123(a)(1)

Final § 111.123(a)(1) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include reviewing and approving all master manufacturing records and all modifications to the master manufacturing records. Final § 111.123(a)(1) derives from duplicate proposed requirements, in proposed §§ 111.37(b)(4) and 111.45(c), with no changes other than the editorial changes associated with the reorganization.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(4) or 111.45(c), but have combined them as final § 111.123(a)(1).

2. Final § 111.123(a)(2)

Final § 111.123(a)(2) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include reviewing and approving all batch production-related records. Final § 111.123(a)(2) derives from proposed § 111.37(b)(5), which would require, in part, the quality control unit to review and approve all batch production-related records. Proposed § 111.37(b)(5) explicitly stated, in part, that the batch record would include, but not be limited to, cross-referencing receiving and batch production records.

(Comment 227) One comment expresses concern that proposed § 111.37(b) does not state specifically that the complete batch history, including batch record, analytical records, quality control records, yields, and packaging records should be reviewed and approved by the quality control unit before the batch is shipped. The comment believes these are important requirements that should be clearly stated.

(Response) Proposed § 111.37(b)(5) would require that the quality control unit "review and approve all batch production-related records, including but not limited to * * *" We disagree with the comment that this proposed provision would not include what the comment describes. To the extent that the comments interpreted the list of records to mean that only the partial listing of records was required, we have modified final § 111.123(a)(2) to require quality control personnel to review all batch production-related records. We do not emphasize any particular aspect of the batch production record. This reduces the potential to misinterpret the requirement as being limited to the specific items cited.

(Comment 228) As already discussed in detail with respect to final § 111.120(a), some comments assert the proposed requirement that the review of the batch record by the quality control unit include cross-referencing of receiving records with the batch production record is redundant to other requirements that the quality control unit review receiving records for components, packaging, and labels. In general, these comments assert the requirement should be completed properly and only once.

(Response) We agree with the comments that the review of records, such as receiving records, if done properly the first time that it is performed, need not be repeated. Therefore, the final rule does not include any requirements for cross-referencing receiving records with the batch production record as we would require under proposed § 111.37(b)(5).

3. Final § 111.123(a)(3)

Final § 111.123(a)(3) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing

operations include reviewing all monitoring required under subpart E. Final § 111.123(a)(3) derives from the following proposed provisions:

- Proposed § 111.35(f) which would require you to monitor the in-process control points, steps, or stages to ensure that specifications established under proposed § 111.35(e) are met and to detect any unanticipated occurrence that may result in adulteration;

- Proposed § 111.35(e)(2) which would require you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration, including the in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary supplements;

- Proposed § 111.35(i)(2) which would require you to review the results of the monitoring required under proposed § 111.35(f) and conduct a material review if an established specification is not met or if there is any unanticipated occurrence that adulterates or could result in adulteration;

- Proposed § 111.35(o)(2) which would require you to make and retain records to ensure you follow the requirements of proposed § 111.35, including the actual results obtained during the monitoring operation; and

- Proposed § 111.37(b)(5) which would require the quality control unit to review and approve all batch production-related records.

Under the final rule, the results of the monitoring required under proposed § 111.35(f) must be kept in the batch record (see the discussion of the batch record in section XIV of this document). Quality control personnel must review the results of the required monitoring.

(Comment 229) One comment suggests the phrase "review the results of the monitoring required by this section" be deleted from proposed

§ 111.35(i)(2) because it is unnecessary and can be read as narrowing any final rule. This comments points out the only required monitoring in the proposal appears in § 111.35(f) related to monitoring of in-process control points, steps, or stages, and that such monitoring would not necessarily find all failures in specifications, for example, specifications related to raw materials or labels.

(Response) We disagree with the comment that the quoted language narrows the final rule. Monitoring that relates to in-process control points, steps, or stages would be required under proposed § 111.35(f) and is now required in final § 111.123(a)(3). However, in practice, a manufacturer must monitor its entire operation to ensure that the requirements of the final rule are met. For example, under final § 111.73, a manufacturer must determine whether specifications established under final § 111.70 are met and under final § 111.75(a) and (f) a manufacturer must use certain criteria to determine whether specifications for components and labels, respectively, are met. Thus, there are sufficient controls in other requirements to ensure the entire production and process controls are functioning as intended.

4. Final § 111.123(a)(4)

Final § 111.123(a)(4) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include conducting any required material review and making any required disposition decision. Final § 111.123(a)(4) derives from the following proposed provisions:

- Proposed § 111.37(b)(5) which, in part, would require the quality control unit to approve a material review and disposition decision related to batch production records; and

• Proposed § 111.50(d)(1) which, in part, would require, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit to conduct a material review and make a disposition decision.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(5) or 111.50(d)(1).

5. Final § 111.123(a)(5)

Final § 111.123(a)(5) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include approving or rejecting any reprocessing. Final § 111.123(a)(5) derives from proposed § 111.37(b)(5) which would require the quality control unit to approve any reprocessing. For consistency with other provisions in this final rule (such as final § 111.90), final § 111.123(a)(5) includes a revision that quality control personnel must approve—or reject—any reprocessing.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(5).

6. Final § 111.123(a)(6)

Final § 111.123(a)(6) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether all in-process specifications established in accordance with § 111.70(c) are met. Final § 111.123(a)(6) derives from the following proposed provisions:

• Proposed § 111.35(f) which would require you to monitor the in-process control points, steps, or stages to ensure specifications are met (including the in-process specifications required under proposed § 111.35(e)(2)) and

- Proposed § 111.37(a) which, in part, would require the quality control unit to ensure your manufacturing, packaging, labeling, and holding operations are performed in a manner that prevents adulteration, including that such operations ensure the dietary supplement meets its specifications for identity, purity, quality, strength, and composition.

Final § 111.123(a)(6) is consistent with the overall approach, set forth in final §§ 111.70, 111.73, and 111.75, that focuses on ensuring the quality of the dietary supplement throughout the production and process control system.

We did not receive comments specific to quality control operations under proposed §§ 111.35(e)(2) or (f), or 111.37(a).

7. Final § 111.123(a)(7)

Final § 111.123(a)(7) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include determining whether each finished batch conforms to product specifications established in accordance with final § 111.70(e). Final § 111.123(a)(7) derives from proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2).

8. Final § 111.123(a)(8)

Final § 111.123(a)(8) requires that quality control operations for the master manufacturing record, the batch production record, and manufacturing operations include approving and releasing, or rejecting, each finished batch for distribution, including any reprocessed finished batch. Final § 111.123(a)(8) derives from the following proposed provisions:

- Proposed § 111.37(b)(5) which, in part, would require the quality control unit to approve batch production records for releasing finished batches for distribution;
- Proposed § 111.50(d)(2) which would require the quality control unit to not approve and release for distribution any batch that does not meet all specifications; and
- Proposed § 111.50(g) which would require the quality control unit to not approve and release for distribution any reprocessed batch of dietary supplement that does not meet all specifications.

We did not receive comments specific to the proposed provisions cited above.

9. Final § 111.123(b)

Final § 111.123(b) requires that quality control personnel must not approve and release for distribution:

- any batch of dietary supplement for which any component in the batch does not meet its identity specification;
- any batch of dietary supplement, including any reprocessed batch, that does not meet all product specifications established in accordance with § 111.70(e);
- any batch of dietary supplement, including any reprocessed batch, that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act; and
- any product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for which sufficient assurance is not provided to adequately identify the

product and to determine that the product is consistent with your purchase order.

Final § 111.123(b) derives from the following proposed provisions:

- Proposed § 111.50(d)(2) which would require the quality control unit to not approve and release for distribution any batch of dietary supplement that does not meet all specifications;
- Proposed § 111.50(g) which would require that a reprocessed batch of dietary supplement meet all specifications and that the quality control unit approve its release for distribution; and
- Proposed § 111.37(b)(11)(iii) which would require the quality control unit to collect representative samples of each batch of dietary supplement manufactured to determine, before releasing for distribution, whether the dietary supplement meets its specifications for identity, purity, quality, strength, and composition.

The final provision clarifies all of the responsibilities of quality control personnel and includes provisions consistent with changes made to final §§ 111.73, 111.77, and 111.90.

We did not receive comments specific to those aspects of proposed §§ 111.50(g) and 111.37(b)(11)(iii) that are relevant to final § 111.123(b). We discuss in the following paragraphs comments we received to proposed § 111.50(d)(2).

(Comment 230) Several comments object to proposed § 111.50(d)(2) because it would prohibit the release of any batch that does not meet all specifications. Other comments suggest the prohibition should apply to meeting "release specifications" or "essential manufacturer specifications"

rather than "all specifications" because in-process deviations and minor deviations may not affect product quality.

(Response) A finished dietary supplement that is ready for release for distribution must meet component specifications for identity established under final § 111.70(b) and all product specifications established for the batch under final § 111.70(e) and must be manufactured in a manner to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. The final rule does not prevent you from establishing additional specifications that do not affect the identity, purity, strength, composition, or contaminant levels of your finished dietary supplement. Such a specification is not a component specification for identity or a product specification that is required under the final rule. Final § 111.123(b) would not preclude you from releasing a product that fails to meet a specification that is not a component specification for identity or a product specification established under final § 111.70 provided quality control personnel approve such release. Final § 111.123(b) would not preclude you from releasing a product that you are permitted to release under final § 111.77.

(Comment 231) Some comments note that proposed § 111.50(d)(2) would not allow the quality control unit to conduct an investigation, and make a disposition decision, of the failure of a batch to meet specifications. These comments assert proposed § 111.50(d)(2) therefore restricts the provision in proposed § 111.50(d)(1) which would require that, if a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision. The comments argue the quality control unit should have the authority to release products with minor deviations.

(Response) As discussed previously (see discussion of final § 111.90 in subpart E in section X of this document), we acknowledge that some specifications, such as component, other than for identity, and in-process specifications, that are not met may be able to be corrected by a treatment or an in-process adjustment. Quality control personnel would need to conduct a material review and disposition decision for any such specification not met. If there are specifications 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 (final § 111.70(a)), you must determine whether these specifications are met (final § 111.73).

Final § 111.123(b) does not preclude you, for example, from releasing a product that was the subject of a material review because sampling procedures had not been followed if, as a corrective action, the appropriate samples were collected and subjected to appropriate tests and examinations.

*K. What Quality Control Operations Are Required for Packaging and Labeling Operations? (Final § 111.127)*

Final § 111.127 sets forth the required operations that quality control personnel must perform with respect to packaging and labeling operations.

1. Final § 111.127(a) and (b)

Final § 111.127(a) and (b) set forth requirements for product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier).

Final § 111.127(a) and (b) apply to product that has left the control of the person who manufactured the batch; for example, the purchase of dietary supplements in bulk for packaging or labeling by a person who will distribute

the packaged and labeled dietary supplements under a private label. If you are a packager or labeler who operates under contract to the manufacturer, and you will return the dietary supplement to the manufacturer, we would not consider that you are "receiving" product within the meaning of final § 111.127(a) and (b). We would consider you to be no different than an operating unit of the manufacturer. In section VI of this document (subpart A), we discuss in detail the scope of this final rule and its applicability to contractors.

a. *Final § 111.127(a).* Final § 111.127(a) requires that quality control operations for packaging and labeling operations include reviewing the results of any visual examination and documentation to ensure that specifications established under final § 111.70(f) are met for product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier). Final § 111.127(a) derives from the following proposed provisions:

- Proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to ensure that dietary supplements you receive are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met and

- Proposed § 111.40(a)(3) which would, in part, require you to quarantine dietary supplements you receive until your quality control unit reviews the supplier's invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met.

Final § 111.127(a) includes revisions associated with final §§ 111.70(f) and 111.75(e) which set forth requirements for all products you receive from a supplier for packaging or labeling as dietary supplements (and for distribution

rather than for return to the supplier). As discussed in section X of this document, under final § 111.70(f) if you receive such product, you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order. In addition, under final § 111.75(e) before you package or label such products, you must visually examine the products and have documentation to determine whether the specifications that you established under final § 111.70(f) are met. The documentation you have to satisfy the requirements of final § 111.75(e) is not limited to a supplier's invoice, guarantee, or certification and, thus, final § 111.127(a) incorporates the standard set by final § 111.75(e) (i.e., documentation) rather than the proposed standard of the supplier's invoice, guarantee, or certification. In addition, consistent with final § 111.75(e), final § 111.127(a) requires quality control personnel to review the results of the visual examination but not otherwise review the results of tests or examinations.

We did not receive comments specific to quality control operations under proposed § 111.40(a)(2) or (a)(3).

b. *Final § 111.127(b).* Final § 111.127(b) requires that quality control operations for packaging and labeling operations include approving, and releasing from quarantine, all products you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier) before the products are used for packaging and labeling. Final § 111.127(b) derives from proposed § 111.40(a)(3) which, in part, would require you to quarantine dietary supplements that you receive until your quality control unit reviews the supplier's invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that

specifications are met, and approves and releases the dietary supplements from quarantine before you use them.

As with final § 111.127(a), final § 111.127(b) includes revisions associated with changes made in final §§ 111.70(f) and 111.75(e).

We did not receive comments specific to quality control operations under proposed § 111.40(a)(3).

2. Final § 111.127(c)

Final § 111.127(c) requires that quality control operations for packaging and labeling operations include reviewing and approving all records for packaging and label operations. Final § 111.127(c) derives from proposed § 111.37(b)(10) which, in part, would require the quality control unit to review and approve all packaging and label records.

We did not receive comments specific to quality control operations under proposed § 111.37(b)(10).

3. Final § 111.127(d)

Final § 111.127(d) requires that quality control operations for packaging and labeling operations include determining whether the finished packaged and labeled dietary supplement conforms to specifications established in accordance with final § 111.70(g). Final § 111.127(d) derives from the following proposed provisions:

- Proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications and

- Proposed § 111.37(b)(11)(iv) which, in part, would require the quality control unit to collect representative samples of each batch of packaged and labeled dietary supplements to determine that you used the packaging

specified in the master manufacturing record and applied the label specified in the master manufacturing record.

For clarity, final § 111.127(d) identifies the specifications as those established in final § 111.70(g).

We did not receive comments specific to quality control operations under proposed § 111.37(b)(2) or (b)(11)(iv).

4. Final § 111.127(e)

Final § 111.127(e) requires that quality control operations for packaging and labeling operations include conducting any required material review and making any required disposition decision. Final § 111.127(e) derives from the following proposed provisions:

- Proposed § 111.70(c) which would require you to conduct a material review and make a disposition decision of any packaged and labeled dietary supplement that does not meet specifications and
- Proposed § 111.40(a)(3) which, in part, would require you, if specifications are not met for a received dietary supplement, to conduct a material review and make a disposition decision.

Final § 111.127(e) includes revisions associated with final § 111.87 which requires quality control personnel to conduct any required material review and make any required disposition decision.

We did not receive comments specific to quality control operations under proposed §§ 111.70(c) or 111.40(a)(3).

5. Final § 111.127(f) and (g)

Final § 111.127(f) requires that quality control operations for packaging and labeling operations include approving or rejecting any repackaging of a packaged dietary supplement. Final § 111.127(g) requires that quality control

operations for returned dietary supplements include approving or rejecting any relabeling of a packaged and labeled dietary supplement. Final § 111.127(f) and (g) derive from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to approve any repackaging and relabeling and
- Proposed § 111.70(d) which would require the quality control unit to approve and document any repackaging or relabeling of a dietary supplement.

For consistency with other provisions in this final rule (such as final § 111.90), final § 111.127(f) and (g) provide that quality control personnel must clearly choose between approving—or rejecting—any repackaged or relabeled dietary supplements.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(10) or 111.70(d).

6. Final § 111.127(h)

Final § 111.127(h) requires that quality control operations for packaging and labeling operations include approving for release, or rejecting, any packaged and labeled dietary supplement (including a repackaged or relabeled dietary supplement) for distribution. Final § 111.127(h) derives from the following proposed provisions:

- Proposed § 111.37(b)(10) which, in part, would require the quality control unit to approve the release of packaged and labeled dietary supplements for distribution; and
- Proposed § 111.70(e) which, in part, would require the quality control unit to approve or reject the release of any repackaged or relabeled dietary supplement.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(10) or 111.70(e).

*L. What Quality Control Operations Are Required for Returned Dietary Supplements? (Final § 111.130)*

Final § 111.130 sets forth the minimum required operations quality control personnel must perform with respect to returned dietary supplements.

Final § 111.130 modifies proposed § 111.85 which set forth requirements for returned dietary ingredients and dietary supplements, including requirements for quality control operations for returned dietary supplements. We did not explicitly include quality control operations with respect to returned dietary supplements under proposed § 111.37 but did include quality control operations in proposed § 111.85 for returned dietary supplements. The provisions of the final rule that pertain to returned dietary supplements are set forth in final subpart N. However, we are duplicating these requirements in subpart F to make clear that once returned products are back within your control, quality control personnel must perform appropriate operations before the products are redistributed, if they are approved for redistribution. Any returned dietary supplements that are reprocessed must be returned to your production and process control system, and, therefore, must be properly reviewed by quality control personnel.

1. Final § 111.130(a)

Final § 111.130(a) requires that quality control operations for returned dietary supplements include conducting any required material review and making any required disposition decision. Final § 111.130(a) differs slightly from proposed § 111.85(a) which, in part, would require the quality control

unit to conduct a material review and make a disposition decision for any returned dietary supplement.

(Comment 232–233) Some comments support the proposed requirement to specify that it is the quality control unit that conducts the material review and makes the disposition decision regarding returned dietary supplement products.

(Response) These comments are consistent with proposed § 111.85(a) which is being incorporated into final § 111.130(a).

2. Final § 111.130(a)(1) and (a)(2)

Final § 111.130(a)(1) requires that quality control operations for returned dietary supplements include determining whether tests or examination are necessary to determine compliance with product specifications established in accordance with final § 111.70(e).

Final § 111.130(a)(2) requires that the review and disposition decision for returned dietary supplements include review of the results of any tests or examinations that are conducted to determine compliance with product specifications established in accordance with final § 111.70(e).

3. Final § 111.130(b)

Final § 111.130(b) requires that quality control operations for returned dietary supplements include approving or rejecting any salvage and redistribution of any returned dietary supplement. Final § 111.130(b) derives from proposed § 111.37(b)(15) which, in part, would require the quality control unit to approve the distribution of returned dietary supplements. As discussed in the preamble to the 2003 CGMP Proposal, "salvage" means to return to distribution without reprocessing (68 FR 12157 at 12215).

For consistency with other regulations in this final rule (such as final § 111.90), final § 111.130(e) provides that quality control personnel must clearly choose between approving—or rejecting—any salvage and redistribution.

(Comment 234) Some comments support the proposed requirement to specify that it is the quality control unit who approves, or rejects, a returned dietary supplement for redistribution.

(Response) These comments are consistent with proposed § 111.37(b)(15) which is being incorporated into final § 111.130(b).

4. Final § 111.130(c)

Final § 111.130(c) requires that quality control operations for returned dietary supplements include approving or rejecting any reprocessing of any returned dietary supplement. Final § 111.130(c) derives from proposed § 111.37(b)(15) which, in part, would require the quality control unit to approve the reprocessing of returned dietary supplements. For consistency with other provisions of this final rule (such as final § 111.90), final § 111.130(c) provides that quality control personnel must clearly choose between approving—or rejecting—any reprocessing.

(Comment 235) One comment argues that the responsibility to decide whether a returned dietary supplement is reprocessed belongs with qualified persons in manufacturing operations, and the only responsibility of the quality control unit is to approve the reprocessed product for distribution.

(Response) We disagree with the comment. An underlying principle of these CGMP requirements is that quality control personnel oversee the design and conduct of manufacturing, packaging, labeling, and holding operations. A decision about when reprocessing is, or is not, appropriate requires oversight.

5. Final § 111.130(d)

Final § 111.130(d) requires that quality control operations for returned dietary supplements include determining whether the reprocessed dietary supplement meets product specifications and either approving for release, or rejecting, any returned dietary supplement that is reprocessed. Final § 111.130(d) derives from the following proposed provisions:

- Proposed § 111.37(b)(2) which, in part, would require the quality control unit to determine whether all dietary supplements conform to specifications; and
- Proposed § 111.65(d) which, in part, would require you, if a material review and disposition decision allows you to reprocess a dietary supplement, to ensure it meets specifications and is approved by the quality control unit.

For consistency with other regulations in this final rule (such as final § 111.90), final § 111.130(d) provides that quality control personnel must clearly choose between approving—or rejecting—a reprocessed dietary supplement.

We did not receive comments specific to quality control operations under proposed §§ 111.37(b)(2) or 111.65(d).

*M. What Quality Control Operations Are Required for Product Complaints? (Final § 111.135)*

Final § 111.135 requires that quality control operations for product complaints include reviewing and approving decisions about whether to investigate a product complaint and reviewing and approving the findings and followup action of any investigation performed.

Final § 111.135 derives from proposed § 111.95 which would set forth requirements for consumer complaints (now "product complaints"), including

requirements for quality control operations for consumer complaints. We did not explicitly include quality control operations with respect to consumer complaints under proposed § 111.37 but did include quality control operations in proposed § 111.95 for review and investigation of consumer complaints. The final rule's product complaint requirements are now set forth in final subpart O. However, we have duplicated the requirements for quality control operations for product complaints in subpart F to make clear that your investigation of the product complaint has the potential to uncover a problem with your production and process control system and, therefore, quality control personnel must exercise appropriate oversight of your investigation of any product complaint.

*N. What Records Must You Make and Keep? (Final § 111.140)*

Final § 111.140 sets forth the requirements for records that quality control personnel must make and keep.

1. Final § 111.140(a)

Final § 111.140(a) requires quality control personnel to make and keep records required under subpart F in accordance with subpart P. Final § 111.140(a) derives from proposed § 111.37(d) with editorial revisions associated with the reorganization.

Other than comments that generally opposed the requirements to make and keep records, and to have records available for inspection and copying by FDA when requested (see the discussion in section V of this document), we did not receive comments specific to proposed § 111.37(d).

2. Final § 111.140(b)(1)

The final rule (final § 111.103) requires you to establish and follow written procedures for the responsibilities of the quality control operations, including written procedures for conducting a material review and making a disposition decision and for approving or rejecting reprocessing. The written procedures are records. Therefore, final § 111.140(b)(1) requires you to make and keep a record of the written procedures for the responsibilities of the quality control operations.

3. Final § 111.140(b)(2)

Final § 111.140(b)(2) requires written documentation, at the time of performance, that quality control personnel performed the review, approval, or rejection requirements under subpart F. Final § 111.140(b)(2)(i) requires quality control personnel to record the date that the review, approval, or rejection was performed. Final § 111.140(b)(2)(ii) requires quality control personnel to record the signature of the person performing the review, approval, or rejection. Final § 111.140(b)(2) derives from proposed § 111.37(c) with revisions associated with the reorganization.

We did not receive comments specific to proposed § 111.37(c).

4. Final § 111.140(b)(3)

Final § 111.140(b)(3) requires quality control personnel to document any material review and disposition decision and followup and include the documentation in the batch record. Final § 111.140(b)(3) derives from proposed § 111.35(j) with revisions associated with the reorganization and a revision, associated with final § 111.87 which requires quality control personnel to conduct the material review and make the disposition decision.

Final § 111.140(b)(3) details the type of information that must be included as part of this documentation. Five paragraphs derive from proposed § 111.35(j)(1) through (j)(5), with editorial changes associated with the reorganization. One paragraph is associated with final § 111.90(b) which requires that you not reprocess any component or dietary supplement that is rejected or treat a component or make an in-process adjustment 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 that is based on a scientifically valid reason and approve the reprocessing, treatment, or in-process adjustment. Another paragraph derives, in part, from proposed § 111.37(c)(2) which would require the signature of the quality control unit person performing the requirement.

The documentation that must be included under final § 111.140(b)(3) is as follows:

- Section 111.140(b)(3)(i)—Identification of the specific deviation or the unanticipated occurrence;
- Section 111.140(b)(3)(ii)—A description of your investigation into the cause of the deviation from the specification or the unanticipated occurrence;
- Section 111.140(b)(3)(iii)—An evaluation of whether the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the dietary supplement or a failure to package and label the dietary supplement as specified in the master manufacturing record;
- Section 111.140(b)(3)(iv)—Identification of the action(s) taken to correct, and prevent a recurrence of, the deviation or the unanticipated occurrence;
- Section 111.140(b)(3)(v)—An explanation of what you did with the component, dietary supplement, packaging, or label;

- Section 111.140(b)(3)(vi)—A scientifically valid reason for any reprocessing of a dietary supplement that is rejected, or the treatment or in-process adjustment of a component that is rejected; and

- Section 111.140(b)(3)(vii)—The signature of the individual(s) designated to perform the quality control operation, who conducted the material review and made the disposition decision, and of each qualified individual who provided information relevant to that material review and disposition decision.

We did not receive comments specific to proposed § 111.35(j).

## 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 of this document, 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 G for written procedures? | N/A |

TABLE 8.—DERIVATION OF SECTIONS IN FINAL SUBPART G—Continued

| Final Rule | 2003 CGMP Proposal |
|---|---|
| § 111.155 What requirements apply to components of dietary supplements? | § 111.40(a)(1) through (a)(5)<br>§ 111.35(d)(1) throug (d)(5) |
| § 111.160 What requirements apply to packaging and labels received? | § 111.35(e)(4)<br>§ 111.40(a)(2) and (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 products that are received for packaging or labeling as a dietary supplement? | § 111.74 |
| § 111.180 Under this subpart G, what records must you make and keep? | § 111.40(c)(1)(i) through (c)(1)(iv) and (c)(2)<br>§ 111.35(d)(4) |

*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 in 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 quality control personnel release 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 of this document. 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) (21 CFR 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 in the previous paragraphs, 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 to proposed § 111.5 and final § 111.5 and are therefore not repeating proposed § 111.35(d)(5) in final § 111.35.

Although we are deleting § 111.35(d) from the final rule, there were several comments that we received, and respond to in the following paragraphs, 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,[10] 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 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

[10]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.

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 food additive means "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food" if the use of such substance is not GRAS (section 201(s) of the act).[11] We have discretion to determine whether an ingredient is 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

[11]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.

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 GRAS Proposal to establish a notification program for the use of GRAS substances (62 FR 18938, 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 (21 CFR 74.101) and FD&C Red No. 40 (21 CFR 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 (21 CFR 73.30) and for beta-carotene (21 CFR 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 21 CFR 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 quality control personnel 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 in the manufacture of a dietary supplement until:

- 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);
- Quality control personnel review and approve the results of any test or examinations conducted on components; and
- Quality control personnel approve 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