X. Comments on Requirement to Establish a Production and Process Control System (Final Subpart E)

A. Reorganization of Proposed § 111.35 Into Final Subpart E

In the 2003 CGMP Proposal, the requirements for a production and process control system were set forth in § 111.35. As shown in table 6, we are reorganizing proposed § 111.35 into subpart E. Table 6 lists the sections in final subpart E and identifies the sections in the 2003 CGMP Proposal that form the basis of the final rule.

Table 6. - Derivation of Sections in Final Subpart E

Final Rule	2003 CGMP Proposal
§ 111.55 What Are the Requirements to Implement a Production and Process Control System?	§ 111.35(a)
§ 111.60 What Are the Design Requirements for the Production and Process Control System?	§ 111.35(b)
§ 111.65 What Are the Requirements for Quality Control Operations?	§ 111.35(c)
§ 111.70 What Specifications Must You	§ 111.35(e),

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Establish?	(f), (g), and (k)
§ 111.73 What is Your Responsibility for Determining Whether Established Specifications are Met?	§ 111.35 (f), (g), and (h)
§ 111.75 What Must You do to Determine Whether Specifications are Met?	§ 111.35(e), (f), (g), (h), (i), (k), and (l) § 111.37 (b)(11(iv) § 111.40(a)(2)
§ 111.77 What Must You do if Established Specifications Are not Met?	§ 111.50(d)(2) § 111.50(f) § 111.50(g) § 111.35(i)(4)(i) § 111.35(i)(4)(ii)
§111.80 What Representative Samples Must You Collect?	§ 111.37(b)(11)
§ 111.83 What are the Requirements for Reserve Samples?	§ 111.37(b)(12) § 111.50(h) § 111.83(b)(2)
§ 111.87 Who Conducts a Material Review and Makes a Disposition Decision?	§ 111.35(i) and (n) § 111.37(b)(5) and (b)(14) § 111.40(a)(3) § 111.50(d)(1) § 111.85(a) and (c)
§ 111.90 What Requirements Apply to treatment, In-process Adjustments, and Reprocessing When There is a Deviation or Unanticipated Occurrence or When a Specification Established in Accordance	§ 111.35(i)(4) § 111.50(d)(1), (f), and (g) § 111.65(d)

with § 111.70 is not Met?	
§ 111.95 Under this Subpart, What Records Must You Make and Keep?	§ 111.35(m) and(o)

B. General Comments on Proposed § 111.35

(Comment 145) Several comments emphasize the first step in ensuring safe, high quality products is to use high quality components that meet well-defined specifications. Some of these comments assert the 2003 CGMP Proposal does not encourage development of such specifications.

Several comments assert that a more appropriate balance is needed between an effective process control system and a reasonable testing scheme that is calculated to confirm the quality of dietary supplements, and that it is important to provide companies with more flexibility in developing a specific CGMP program that satisfies the requirements. The comments stress it is important to build quality into a product throughout the entire production process by relying on strong process controls rather than by testing at the finished batch stage. One comment asserts that, in an appropriate process control system, testing is a means to monitor and ensure that the control system is functioning as intended. Many comments recommend the final rule include rigorous in process controls plus a requirement for

one identity test of incoming components to ensure quality and safety.

Many comments assert a certificate of analysis can be a key element of the manufacturing process provided that a manufacturer certifies that a vendor consistently supplies suitable product through a combination of vendor audits and product testing. (A certificate of analysis is a document, provided by the supplier of a component prior to or upon receipt of the component, that documents certain characteristics and attributes of the component.) Comments also assert that, with use of a certificate of analysis from a properly qualified supplier, the amount of required testing could be reduced. One comment notes that, although a certificate of analysis may not be relied upon completely to forgo testing of a received ingredient, the extent of testing could be reduced to take into account the history of the supplier in providing quality ingredients. This and other comments recommend the dietary supplement manufacturer conduct identity tests to ensure that the correct component has been received. A few comments note that the drug CGMP regulations permit the use of a supplier's certificate of analysis based upon certification of the supplier by a program of complete testing for conformance with the certificate of analysis.

Several comments support the use of a qualified supplier's certificate of analysis in lieu of testing at the finished batch stage. One comment recommends testing be strategically employed to verify that other control procedures have accomplished their intended result; if other controls are adequate, a statistically-based testing program should be permitted for finished batches rather than the proposed requirement for testing every batch for every specification.

Many comments note that section 402(g)(2) of the act directs us to develop dietary supplement CGMP requirements that are modeled after the CGMP regulations for food. These comments point out that, because the food CGMPs allow the use of a verified certificate of analysis, it is unfair and illogical to disallow a certificate of analysis in the dietary supplement CGMP final rule. One comment states the proposed requirements for production and process controls are more stringent than the requirements for drug products.

Several comments stress that the most critical aspect of a successful CGMP system is effective process control, which includes a requirement for written procedures and documentation for all key processing operations. Many comments argue that effective process control, including extensive written

procedures, should allow for a decreased testing burden with respect to the finished product. One comment suggests we exempt manufacturers from the requirement to test each batch of finished product if they have a qualified manufacturing process that meets certain basic criteria, including a requirement for written procedures for each stage of the process and a written plan for qualifying this process.

Several comments urge us to build more flexibility into the testing requirements, in both the type and number of tests required and the point(s) in the supply chain at which they would be required. Some comments recommend that the frequency of testing be established under a statistically valid method to ensure that in-process controls are adequate to guarantee production of a safe and effective dietary supplement or ingredient. Several comments recommend we require manufacturers to test incoming ingredients and raw materials, in lieu of testing each finished batch of product. These comments state it is more prudent to test to ensure that the materials used in formulating a product are appropriate and safe than to risk making an adulterated product and, in so doing, contaminate manufacturing equipment.

Several comments recommend we allow manufacturers to employ

skip-lot testing as an alternative to testing each finished batch of product. One comment states that, with adequate process controls in place, periodic or skip-lot testing is sufficient, and notes that skip-lot testing is acceptable under the regulatory frameworks for herbal products in other countries, including Canada and countries in the European Union.

In summary, the comments suggest an approach that stresses the importance of establishing specifications for components, relying on a certificate of analysis from a qualified supplier for certain specifications with qualification of the suppliers, and establishing and following written procedures. This overall approach would focus on building quality into a dietary supplement throughout the production and process control system. The role of testing at the finished batch stage would become a check on whether the overall manufacturing process is, in fact, under control.

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(Response) Based upon a review of the comments, we have reconsidered the approach taken in the 2003 CGMP Proposal. The 2003 CGMP Proposal would require that all finished batches of dietary supplements be tested at the finished batch stage to ensure that the products met specifications for identity, purity, strength and composition. The 2003 CGMP proposal recommended,

but would not require, testing of incoming components to ensure that component specifications, including identity, were met. However, if a specification (such as identity) could not be tested at the finished batch stage, the proposed rule would require a firm to test incoming components for that specification and to test for that specification at the in-process stage as necessary to ensure that products met specifications. We are persuaded that, as an alternative to testing each finished batch of product, we can allow for the use of a statistically sound sampling and testing program for finished batches of dietary supplements unless a manufacturer chooses to test every batch. Such a sampling and testing program is feasible when controls are implemented earlier than the final product stage in the manufacturing process. Controls include the use of a certificate of analysis from a qualified supplier for specifications other than the identity of a dietary ingredient, and the establishment and monitoring of in-process manufacturing controls. We agree with the comments that if we reduce the requirements for testing at the finished batch stage, then it is critical that you determine whether components meet specifications. We address this issue in the following two ways: (1) Each manufacturer must confirm the identity of each component prior to use (you must

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test or examine dietary ingredients to verify the identity, but may rely on a certificate of analysis to confirm the identify of components other than dietary ingredients); and (2) each company must confirm other required specifications for components prior to use, either by relying upon a certificate of analysis or by testing or examining the component.

As the comments have suggested, specifications for the "identity" of components of dietary supplements are critically important. These comments included references to industry proposals that supported identity testing. The 1997 ANPRM (62 FR 5700) included an industry proposed outline of CGMP provisions which contained a provision that required identity testing as follows:

> (iv) Each lot of raw material shall undergo at least one test by the manufacturer to verify its identity. Such tests may include any appropriate test with sufficient specificity to determine identity, including chemical and laboratory tests, gross organoleptic analysis, microscopic identification, or analysis of constituent markers.

60 FR 5700 at 5705.

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In January 2004, a group of trade associations representing dietary supplement manufacturers and others submitted text of

proposed CGMP requirements to the docket as an alternative to the 2003 CGMP Proposal. This submission also included a provision which required identity testing as follows:

> (1) For components, dietary ingredients, or dietary supplements that you receive, you must:
>
> (i) conduct at least one test or examination to verify that the specifications for identity are met;. . .

96N-0417-EMC000261-02 at 20.

Both the 1997 ANPRM industry outline and the January 2004 industry docket submission included provisions that allowed certificates of analysis to establish specifications other than for identity for ingredients and components.

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In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12162), we discussed a case in which ***Digitalis lanata*** was labeled as plantain and, as a result, a young woman experienced a life-threatening abnormal heart function after consuming a dietary supplement containing ***Digitalis lanata*** in lieu of plantain. The problem occurred notwithstanding the fact that certificates of analysis furnished by the supplier provided assurances that the component was indeed plantain.

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Because of the critical importance of ensuring the proper identity of dietary ingredients -- they are the central defining

ingredients of a dietary supplement -- we are requiring each firm that uses a dietary ingredient to perform its own testing or examination for identity of each dietary ingredient prior to use. This requirement is similar to the proposed requirement set forth by industry in both the 1997 ANPRM and in the January 2004 industry comment to the proposed rule. Firms may not rely upon a certificate of analysis provided by suppliers to determine the identity of a dietary ingredient before use. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an Interim Final Rule published elsewhere in this FEDERAL REGISTER, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met.

In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12198), we explained that we would not permit firms to rely upon supplier certifications. The decision was based, in large part, on problems that have occurred with faulty certificates in the past. We have, however, reconsidered our position on certificates for specifications, other than for the identity of the dietary ingredients, based on comments discussing how firms have taken steps to ensure that their certificates are reliable. We believe that the minimum criteria that we are establishing for a certificate of analysis, together with the requirement that a firm relying on a certificate of analysis must qualify a supplier and periodically repeat that qualification process, can prevent the problems that have occurred with faulty certificates in the past. Therefore, for component specifications, other than the identity of a dietary ingredient, including confirming the identity of components that are not dietary ingredients, we are permitting firms to rely upon certificates of analysis provided by suppliers, if the certificates meet the requirements of the final rule. Under final § 111.75(a), a firm may rely upon a certificate of analysis from its supplier of a component, provided that certain criteria are met which include the following: (1) The firm first qualifies the supplier by

establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations; (2) the certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations; (3) the firm maintains documentation of how it qualified the supplier; (4) the firm periodically reconfirms the supplier's certificate of analysis; and (5) the firm's quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

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As we discussed in the preamble to the 2003 CGMP Proposal, in-process controls are necessary to ensure that dietary supplements are manufactured in accordance with their specifications (68 FR 12157 at 12197). Under final § 111.75(b), firms must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of the dietary supplement to: (1) Determine whether the in-process specifications are met; and (2) detect any deviation or unanticipated occurrence that may result in a failure to meet specifications. In addition, we have strengthened the requirements for in-process controls by requiring that quality

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control personnel conduct all required material reviews and make all required disposition decisions using written procedures to ensure that deviations or unanticipated occurrences that occur are consistently handled.

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Because of the strengthened requirements regarding component and in-process specifications, the final rule permits testing of a subset of finished batches rather than requiring testing of each finished batch. Consistent with several suggestions in the comments, we built more flexibility into the testing requirements so that a firm may test a subset of finished dietary supplement batches that the firm identifies through a sound statistical sampling plan for selected specifications rather than test every batch of the finished dietary supplement for every specification. Finally, quality control personnel must review and approve any exceptions from testing requirements that are allowed under the rule and the basis for such exceptions. This approach is consistent with the comments that we received and will achieve a high degree of integrity in the manufacturing process, while at the same time provide flexibility to the industry.

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Additional discussion on the requirements for identity testing of dietary ingredients and the appropriate reliance on a certificate of analysis for components other than dietary

ingredients is found in this section in response to comment 174.

C. Final Subpart E and Highlights of Changes to the Proposed Regulations

1. Revisions

The provisions in final subpart E reflect that the final rule applies only to persons who manufacture, package, label, or hold a dietary supplement unless subject to an exclusion in final § 111.1. The approach that we are incorporating into the final rule requires changes in most of the individual paragraphs of proposed § 111.35.

D. What Are The Requirements to Implement a Production and Process Control System? (Final § 111.55)

Final § 111.55 requires you to implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplement to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.55 derives from

proposed § 111.35(a).

(Comment 146) A few comments say the production and process controls outlined in proposed § 111.35 are critical in ensuring that dietary supplements meet specifications for identity, purity, quality, strength and composition. One comment recommends proposed § 111.35(a) be revised to state "* * * that covers all stages of manufacturing, packaging, labeling, and holding of * * * dietary supplements that occur in your facility or for which you otherwise have responsibility." This comment explains that the production of dietary supplements is often broken up into several stages which are under the control of different entities. The comment gives the following examples: a marketing company may manufacture and package a product itself; or it may contract with one company to manufacture and package the product; or it may contract with one company to manufacture the product and another company to package the product; and contract manufacturers and packagers may subcontract portions of the manufacturing or packaging.

(Response) We decline to revise the rule as suggested by the comments. As we discussed in response to comment 37 in section VI, you must comply with the CGMP requirements that apply to your operations related to the manufacturing, packaging,

labeling, and holding of dietary supplements. We decline to include codified language that may not capture all of the possible relationships that exist in a given operation.

E. What Are the Design Requirements for The Production and Process Control System? (Final § 111.60)

Final § 111.60(a) requires that your production and in-process control system be designed to ensure that the dietary supplement is manufactured, packaged, labeled, and held 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. Final § 111.60(b) requires that the production and in-process control system include all requirements of subparts E through L of part 111 and be reviewed and approved by quality control personnel. Final § 111.60(a) and (b) derive from proposed § 111.35(b).

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As discussed in section III, we are clarifying a number of provisions that did not explicitly identify labeling as an operation that is covered by the rule. Final § 111.60 is one such provision. Under proposed § 111.35(a) we would require that

you implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary supplements. In an oversight, proposed § 111.35(b) would require your production and in-process control system to be designed to ensure that the dietary supplement is manufactured, packaged, and held -- but not labeled -- in a manner that would prevent adulteration of the dietary supplement. To correct this oversight, final § 111.60 explicitly identifies labeling as an operation that the design of your production and process control system must address.

(Comment 147) A few comments recommend that the phrase "designed to ensure" in proposed § 111.35(b) be deleted because it requires that formal, prospective studies (similar to a process validation) must be performed and such a requirement would be unduly burdensome.

(Response) We disagree with the comments' interpretation of the proposed regulation and decline the request. Final § 111.60(a) relates to the overall design of your production and process control system. It does not require validation based on scientific studies, but rather that your process contain all the controls necessary to ensure the quality of your dietary supplements and that the dietary supplement is packaged and

labeled as specified in the master manufacturing record. The process, for example, must ensure that the dietary supplement meets all specifications established under § 111.70(e).

F. What Are the Requirements for Quality Control Operations? (Final § 111.65)

Final § 111.65 requires that you implement quality control operations in your manufacturing, packaging, labeling, and holding operations for producing the dietary supplement to ensure that these operations are performed in a manner that ensures the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.65 derives from proposed § 111.35(c).

Proposed § 111.35(c) referred to the role of the quality control unit in manufacturing, packaging, and label operations - but not in holding operations. This was an oversight. We, therefore, revised proposed § 111.35(c) to include "holding" as an operation that is subject to the oversight of quality control personnel for consistency with final § 111.105 (proposed § 111.37(a)), which provides for the performance of quality

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control operations to "ensure that your manufacturing, packaging, label, 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."

(Comment 148) One comment recommends proposed § 111.35(c) be revised to state "ensures that the *** dietary supplement meets manufacturing specifications for identity, purity, quality, strength, and composition."

(Response) We are not making this change because it is unnecessary in the context of the provisions of final § 111.65.

(Comment 149) One comment argues that proposed § 111.35(c) is too wordy and needs clarification. The comment recommends it be revised to state "You must use a quality control unit to ensure that the dietary supplement meets specifications for identity, purity, quality, strength, and composition."

(Response) We disagree with this comment. The change requested by the comment would emphasize a single responsibility of quality control personnel (i.e., releasing final product) and would obscure the fact that quality control personnel have a role in the design and conduct of most of your operations.

(Comment 150) One comment recommends proposed § 111.35(c) be revised to state "ensures that the * * * dietary supplement

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meets specifications for identity, purity, quality, strength, and composition as appropriate to protect the public health; and quality, strength, and composition as appropriate for the * * * product." This comment states it is confusing and unnecessary to require that all five of these attributes be addressed for all dietary supplements. The comment also states the term "purity" requires explanation because not all ingredients or supplements are subject to the same types of contamination.

(Response) We are not making any changes in the provision as suggested by this comment. The comment provides no basis for the assertion that the proposed requirement to use a quality control unit to ensure that a dietary supplement meets specifications for identity, purity, strength, and composition is confusing and unnecessary. In section VI, we explain that purity means that portion or percentage of a dietary supplement that represents the intended product.

G. What Specifications Must You Establish?

(Final § 111.70)

Final § 111.70 derives from proposed §§ 111.35(e), (f), (g) and (k), 111.37(b)(11)(iv), and 111.70(c).

(Comment 151) Some comments state proposed § 111.35(k),

which would require that you test or examine components and dietary supplements for those types of contamination that may adulterate or lead to adulteration, is more appropriate for, and should be incorporated into, proposed § 111.35(e) which would require, in part, that you establish specifications for the identity, purity, quality, strength, and composition of components that you receive and of dietary supplements that you manufacture. The comments note this suggestion would help simplify and eliminate some redundancy in proposed § 111.35. One comment would revise proposed § 111.35(k) to state "Purity specifications for purchased or manufactured components and dietary supplements must be established for those types of contamination which can reasonably be expected to affect the component, ingredient, or supplement in question***." According to the comment not all ingredients or supplements are subject to the same types of contamination, and it would be unduly burdensome to require that all ingredients and supplements be tested for all possible contaminants (as opposed to all likely contaminants).

(Response) We agree that not all ingredients or dietary supplements are subject to the same types of contamination. It would not be practicable or necessary to require testing for all

possible contaminants for every dietary supplement, or for every component used to manufacture a dietary supplement. As we explained in the 2003 CGMP Proposal (68 FR 12157 at 12199-200), the manufacturer has the responsibility to determine what types of contamination are likely or certain to contaminate a given product and to determine what types of tests to conduct and when to test for such contamination. We explained that botanicals are likely or certain to contain filth and microorganisms of public health significance based on the areas in which they are harvested (*id.*) As another example, fungal growth on a botanical component can provide the environment for mycotoxin production, especially aflatoxin (*id*). If fungal growth is present, the manufacturer would need to perform an appropriate test that can detect the toxic substance. We stated that the manufacturer must be aware of potential contamination, regardless of whether due to filth, insects, microorganisms, or toxins and to test or examine, as appropriate, the components and dietary supplements for those types of contamination that may adulterate or that may lead to adulteration (*id.*) Thus, the types of contamination that we were referring to in proposed § 111.35(k) are those that are likely or certain to be present in or on components received, based on the nature of the product, its source, handling prior to receipt by

the facility, or other reason, and not due to poor manufacturing practices that resulted in their presence in the first instance.

It is the responsibility of the manufacturer to identify those contaminants and to establish limits to prevent adulteration under sections 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act. For example, if you manufacture a polysaccharide that derives from seaweed, it is likely that you would include a limit on cadmium, because cadmium is a common contaminant that can be present in marine-derived ingredients. If you manufacture a polysaccharide that has a composition similar to seaweed-derived polysaccharide, but derives from a land-based plant, it is not likely that you would include a limit on cadmium, because cadmium is not a common contaminant of land-based plants. Likewise, if you manufacture a mineral that contains phosphates, it is likely that you would include a limit on arsenic, because phosphates are generally mined and arsenic is a common contaminant that can be present in ingredients that are mined. If you manufacture a mineral that does not include ingredients that are mined, it is not likely that you would include a limit on arsenic.

We agree that controlling contamination is critical to the quality of the dietary supplement. However, we do not agree that

the types of contamination addressed by proposed § 111.35(k) should be considered as a purity specification. We have described purity in this final rule to mean something that you intend to be present in the final product. As explained in section VI, purity means that portion or percentage of a dietary supplement that represents the intended product. For example, you may manufacture a dietary supplement that uses a natural product such as fish oil to provide triglycerides that are a source of the polyunsaturated fatty acids DHA and EPA. The purity refers to the percent of the fish oil that is triglycerides. (Note that if you are manufacturing fish oil to provide the fatty acids DHA and EPA in the dietary supplement, the component specifications for the fish oil must include a strength specification for DHA and EPA in whatever amount you determine is necessary to meet the specification for strength of DHA and EPA in the dietary supplement.) If the natural product also contains lead, or other unwanted ingredients that may adulterate or may lead to adulteration, you would have to establish limits for such contaminants. Thus, to distinguish the proposed requirement in § 111.35(k), which relates to contaminants that may be present on or in the components that you receive, from the requirements related to specifications for

desired characteristics of identity, purity, strength, and composition, we are including a separate requirement on establishing limits on such contaminants for components that you receive (final § 111.70(b)). We also include a requirement for establishing an in-process specification for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met, as necessary, for limits on contamination. In addition, we are including a requirement for such limits on contaminants in the finished batch of dietary supplement (or subset of finished batches) (final § 111.70(e)) to ensure that the manufacturing process has not adversely affected such levels, *e.g.*, has not contributed an additional source of such contaminant or failed to remove the contaminant, when necessary. Such limits would need to ensure the quality of the dietary supplement; i.e., to ensure that the dietary supplement has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under sections 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Thus, in addition to the presence of contaminants that may be in or on components that you receive, there may be sources of contamination that you need to control for in your facility. As discussed in this section, you must establish specifications

under final § 111.70(a) and (c) to prevent adulteration from such sources. The specifications established under final § 111.70(a) and (c) may or may not include limits on such contaminants. By "limits on those types of contamination" in final § 111.70, we do not mean contamination from, for example, the presence of rodent pellets or other filth that would constitute an insanitary condition under sections 402(a)(3) or (a)(4) of the act, if such filth was present in your facility. You are not allowed to establish specifications for limits on contaminants that would otherwise adulterate your product under the act if such contaminants were present.

Further, in proposed § 111.35(k), we included a listing of the types of contamination we considered to be applicable to dietary supplements (68 12157 FR at 12258). We stated that the types of contamination include; (1) filth, insects, or other extraneous material; (2) microorganisms; and (3) toxic substances. We have deleted the listing of the types of contamination in the final rule because the listing is simply informative and establishes no independent requirement. We received several comments, discussed below, on the types of contamination that may be present, some which were solicited by us in the 2003 CGMP Proposal (68 FR 12157 at 12179-81).

In the 2003 CGMP Proposal, we solicited comment on whether we should include in the final rule specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients, because animal-derived dietary ingredients present important public health and safety issues.

In the 2003 CGMP Proposal, the example we used was an animal-derived dietary ingredient potentially contaminated with the agent that causes bovine spongiform encephalopathy (BSE), which is a type of transmissible spongiform encephalopathy (TSE). TSEs are fatal, neurodegenerative disorders, which have been identified in humans and a number of animal species (e.g., cattle, sheep, goats, elk, deer, cats, and mink), but primarily in ruminants (cattle, sheep, elk, deer) (69 FR 42255 at 42256 (July 14, 2004)). Most scientists believe that variant Creutzfeldt-Jakob Disease (vCJD), a progressive neurological disease in humans, is caused by consumption of cattle products contaminated with the agent that causes BSE (69 FR 42255 at 42257).

In the 2003 CGMP Proposal (62 FR 12157 at 12180), we stated that we had communicated with the public and manufacturers of FDA-regulated products about appropriate steps to increase product safety and minimize the risk of products contaminated

with the BSE agent. We referenced a notice in the FEDERAL REGISTER of August 29, 1994 (59 FR 44591), entitled "Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products." We sent letters to dietary supplements manufacturers to alert them to the developing concern about TSEs in animals and Creutzfeldt-Jakob Disease in humans. We recommended they investigate the source of any bovine and ovine material used in their products. We suggested that manufacturers develop plans to ensure, with a high degree of certainty, that bovine and ovine materials used in their products were not from BSE countries or from sheep flocks (foreign or domestic) infected with scrapie. We stated that our Center for Biologics Evaluation and Research (CBER) had developed guidances for industry that describe steps manufacturers should take to ensure the safety and suitability for human use of animal-derived biologics. We also stated that we were considering whether the procedures that CBER recommends for a product with animal-derived materials, substances, or tissues would be appropriate for dietary ingredients and dietary supplements that contain animal-derived materials, substances, or tissues. We believed that the use of an animal-derived material, substance, or tissue in a dietary supplement may raise many of the same serious public health and

safety issues as animal-derived materials, substances, or tissues, in a biologic. We invited comment on whether there is a scientific basis for us to treat animal-derived dietary ingredients in a manner different from, or that would offer less protection than, what is recommended for animal-derived biologics when the same public health and safety risks may be present.

(Comment 152) Several comments state there should not be specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients because BSE issues are not specific to dietary supplements, and because other guidance and regulations, issued by FDA and by the U.S. Department of Agriculture (USDA), already address BSE and public health. Other comments state it would be appropriate to include specific CGMP requirements for BSE as long as the requirements reflect the thinking in currently existing regulations and guidance.

Several comments do not support the need for additional provisions regarding the handling of imported animal-derived ingredients because the industry has already taken steps to comply with the requirements or recommendations issued by either USDA or FDA. The comments state that the regulations issued by USDA for meat related products in the food industry provide adequate control over the use of animal tissues that might

contain microorganisms, specifically viruses, of public health concern.

One comment argues that if purchases of domestic raw tissues have been inspected by USDA, it is unfair to impose additional regulations simply because these tissues are included in dietary supplements. This comment asserts it would be unfair to require testing of animal-derived products given the fact that there are no tests for BSE available; and that reliance on USDA and FDA is the best way to stop the spread of BSE.

Another comment states that industry trade associations have been working actively with their member companies to ensure adherence to the requirements set forth in our various letters regarding the need to develop plans "that ensure, with a high degree of certainty" that animal-derived ingredients are used only in accordance with FDA and USDA policies designed to protect against BSE. The comment states that a summary of industry procurement and handling practices regarding animal-derived ingredients (submitted to us) contains lists of animal-derived ingredients used by various companies, with examples of the certificates of origin and other documentation required for import of any animal-derived materials. One comment states that industry members who handle animal-derived ingredients already

have implemented many of the controls that originated either from USDA or the dietary ingredient suppliers in response to demands by various governments or consumers, and that such matters should remain with USDA to avoid duplication of effort.

Some comments oppose any recommendation that guidance issued by CBER for ensuring the safety and suitability for human use of animal-derived biologics apply to dietary supplement products. One comment includes a review of literature on BSE and claims the review justifies not applying the CBER guidances on BSE to dietary supplement products under part 111.

(Response) For cattle derived materials, you must comply with the requirements of the interim final rule on Bovine Spongiform Encephalopathy (BSE) set forth in § 189.5 (See 70 FR 53063 (September 7, 2005)) and any subsequent modifications. Under the interim final rule, no human food, including dietary supplements, shall be manufactured from, processed with, or otherwise contain, prohibited cattle materials as defined in the rule. In addition, manufacturers and processors of such food that is manufactured from, processed with, or otherwise contains, cattle material must make existing records relevant to compliance available to us for inspection and copying. For both cattle-derived and other animal-derived materials, you must comply with

all applicable provisions of this final rule. For example, under final § 111.70, you must establish specifications for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement. Thus, you must establish specifications for your animal-derived materials that are necessary to ensure the quality of the dietary supplement. Ensuring quality includes preventing contamination that may adulterate the product under 402(a)(1), (a)(2), (a)(3), or (a)(4) of the act. In addition, you must take actions to determine whether the specifications are met (final § 111.73). Therefore, if you used animal-derived materials other than prohibited cattle materials subject to the BSE interim final rule, you would need to establish specifications necessary to ensure the quality of the dietary supplement.

The guidances issued by CBER are still in effect for animal-derived biologics, and we continue to recommend that you use them as appropriate for your products that contain animal-derived ingredients.

(Comment 153) One comment agrees with the provisions of proposed § 111.35(k) but requests that we provide guidance to the industry on allowable limits for the types of contamination listed. Another comment asks us to develop specific DALs for

dietary supplements as more information becomes available, rather than rely on existing DALs from the food industry.

(Response) In the 2003 CGMP Proposal (68 FR 12157 at 12163), we stated that we were not identifying DALs for the types of contaminants for dietary ingredients because there are not enough data available to identify an appropriate DAL for most dietary ingredients. These comments do not provide data, or evidence that data are available, to enable us to issue guidance for DALs for specific contamination. Therefore, we are not taking the action requested by these comments. We discuss DALs in this section in response to comment 157.

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(Comment 154) Some comments suggest the provisions in proposed § 111.35(k), testing for contamination that could adulterate a product, would be more appropriate to include in proposed § 111.35(e), which concerns the establishment of specifications.

(Response) We agree with these comments and are including requirements to include limits on contamination in final § 111.70. The requirements set forth in final §§ 111.70 and 111.75 are consistent with this comment. Under final § 111.70(b) you must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of

the dietary supplement to ensure the quality of the dietary supplement. Under final § 111.70(c) you must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements, and as necessary, limits on contamination for those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Under final § 111.70(e), you must establish product specifications for the identity, purity, strength and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement to ensure the quality of the dietary supplement. As we explained in the response to comment 151, by "limits on those types of contamination" in final § 111.70, we do not mean contamination from, for example, the presence of rodent pellets or other filth that would constitute an insanitary condition under sections 402(a)(3) or (a)(4) of the act, if such filth was present in your facility. You are not allowed to establish specifications for limits on contaminants that would otherwise adulterate your

product under the act if such contaminants were present.

(Comment 155) Several comments object to proposed § 111.35(k) because the provision would be more stringent than the food or drug CGMP requirements. Some point out that the consumption levels for food are higher than for dietary supplements. A few comments argue that proposed § 111.35(k) is too broad as it requires testing or examination for those contaminants that "may" adulterate or "may lead to" adulteration, which could be interpreted to mean testing for unknown contaminants of every description. The comments suggest that this provision be revised to require testing or examination for those types of contamination that "may be present in an amount or at a level" that may adulterate or lead to adulteration or that "may reasonably be expected" to adulterate or lead to adulteration. Other comments agree that to test for all possible contaminants would be burdensome.

Several comments state that manufacturers should be allowed to rely on a supplier's certificate of analysis and that testing should not be required for every potential contaminant. One comment recommends that CGMPs should be specific to the source and that testing should depend on the nature of the material.

Some comments note that for botanicals it is sometimes

nearly impossible to identify and analyze all naturally occurring substances.

(Response) The final rule does not include any specific requirements to test or examine components or dietary supplements for contamination. Rather, under final § 111.70(b) (c), and (e), you are required to establish specifications for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Under final § 111.73, you must determine whether the specifications established under § 111.70 are met. Final § 111.75(a) through (d) sets forth the criteria you must use to determine whether the specifications that you establish under final § 111.70(b), (c), and (e) are met. Consistent with these comments, under final § 111.75(a) you may rely on a certificate of analysis (other than for the identity of a dietary ingredient) from a qualified supplier of components to ensure that specifications that include limits on contamination are met, provided you satisfy the criteria set forth in final § 111.75(a). This would include, for example, relying on a certificate of analysis to ensure that the level of lead in each of your components would not adulterate the dietary supplement.

In determining compliance with the requirements to set

limits for those types of contamination that may adulterate the dietary supplement or lead to adulteration for received components, we would not expect you to set limits for every potential contaminant or for every naturally occurring constituent of a botanical. Rather, we agree with the comments that the substances you would consider when determining whether to set limits for particular types of contamination would vary depending on the source of a component, such as a plant source, an animal source, a microbial source, or a marine source.

(Comment 156) Some comments point out that some compounds, such as mycotoxins, that are toxic at higher levels are detectable in nearly all plant ingredients and are found in the food supply. A few comments assert that dietary ingredients should not contain levels of certain toxic compounds that are higher than reasonable or higher than recognized maximum allowable limits as opposed to the zero tolerance for toxic compounds contained in the 2003 CGMP Proposal.

One comment requests clarification of the term "toxic substances." One comment points out that information for identifying potential adulterants is provided in monographs. Another comment requests clarification on whether dietary supplement manufacturers will be required to test for toxins

while food manufacturers, who may use some of the same ingredients, will not.

(Response) As the comments point out, the food supply does contain some degree of contaminants such as mycotoxins that can be found, for example, in certain grain. We do not have a "zero tolerance" policy for such unavoidable contaminants but we have issued some regulations and guidance to address certain common contaminants. We also have issued a booklet entitled "Action Levels For Poisonous Or Deleterious Substances In Human Food And Animal Feed" (Ref. 30; available at http://www.cfsan.fda.gov). The booklet is a useful resource for manufacturers who seek information about common contaminants that may adulterate a dietary supplement product or lead to adulteration. Another resource is the Foods Chemical Codex,[1] which includes monographs on many substances, such as salts that are used as sources of minerals used in both dietary supplements and conventional food. These monographs include limits on common contaminants, such as

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[1] The Food Chemicals Codex (FCC) project is an activity of the Food and Nutrition Board of the Institute of Medicine. The FCC was intended to provide standards for the purity of food chemicals and thus promote uniform quality and ensure safety in the use of such chemicals. The First Edition of the resulting FCC, published in 1966, was limited to chemicals added directly to foods to achieve a desired technological function. Succeeding editions upgraded the specifications for these substances and added specifications for substances that come into contact with foods and some that are regarded as foods, rather than as additives. The FCC is available for purchase at 1-800-624-6242 or at www.nap.edu.

lead or other heavy metals. In addition, the regulations in part 109 provide information about certain contaminants.

(Comment 157) One comment recommends that all finished products be tested for microorganisms. Another comment contends the manufacturer should be allowed to restrict testing to the raw material if the facility and equipment are monitored for contamination. Some comments point out that contaminants may be detectable in raw materials but not in the finished product.

(Response) We disagree that all finished products must, as a matter of course, be tested for contamination with microorganisms. Whether it is necessary to test the finished product for microorganisms would depend, for example, on the characteristics of your product, the nature and source of your components, the specifications you establish for microbial contaminants in your components and whether these specifications are addressed in a certificate of analysis, the in-process specifications you establish, and the nature of your manufacturing process. However, these comments raise an important point -- i.e., that microbial contamination could occur at your facility even if an incoming component is free of microorganisms. Final subpart K, section XVI, sets forth requirements for your manufacturing operations. Many of these

requirements are designed to limit the potential for contamination with microorganisms.

(Comment 158) Some comments would revise the requirements for establishment of specifications for in-process controls (proposed § 111.35(e)(2)) and the finished batch of dietary supplements (proposed § 111.35(e)(3), so that specifications for attributes of quality, strength, and composition are not required for a product that does not purport to possess such attributes.

(Response) We decline to reword the provision as requested by these comments. The requirement to establish specifications for strength and composition relate to the manufacturers' responsibility to know what their finished dietary supplement is composed of so that their products are consistently manufactured. Establishing specifications and following these CGMP requirements will help ensure the quality of the dietary supplement. The requirement to establish specifications is not limited to when a manufacturer purports that its product possesses attributes of strength and composition on the label. As discussed in the 2003 CGMP Proposal (68 FR 12157 at 12162), the absence of minimum standards has contributed to the adulteration and misbranding of dietary supplements because of contaminants or because manufacturers do not set and meet specifications for their

products, including specifications for identity, purity, strength, and composition and do not set and meet limits on contaminants, when necessary. The comment does not persuade us otherwise. We note, however, that the final rule's requirements to establish specifications for components do, in fact, provide flexibility so that you are not required to establish a component specification for certain attributes, such as the strength of a tablet coating agent (see the discussion of final § 111.70(b) in this section).

(Comment 159) One comment asks for guidance as to what constitutes an official or scientifically valid standard for specifications.

(Response) We are not aware of any officially recognized standard for specifications. Specifications are critical standards that are proposed and justified by the manufacturer for each product that the manufacturer produces. The manufacturer establishes the set of criteria to which a product should conform to be considered acceptable for its intended use. In general, a specification may include a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.

(Comment 160) One comment asks that we clarify whether every specification sheet must include separate, specific qualitative or quantitative standards, and tests to be established for each attribute, or whether a specification sheet can be modeled after a compendial monograph. Some comments state that product specification sheets should be modeled after pharmacopoeia monographs other than those listed in the preamble to the 2003 CGMP Proposal.

(Response) These CGMP requirements do not establish any requirements to have a "specification sheet." Rather, the final rule (final § 111.70(a)) requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. We require that you establish specifications for components (final § 111.70(b)), in-process production (final § 111.70(c)), labels and packaging (final § 111.70(d)), the finished batch of dietary supplement (final § 111.70(e)), product that you receive from a supplier for packaging and labeling (final § 111.70(f)), and the packaging and labeling for the finished packaged and labeled dietary supplement (final § 111.70(g)). The general requirement

for establishing specifications in final § 111.70(a) includes specifications, not otherwise required in final § 111.70(b) through (g), that the manufacturer determines are necessary to achieve quality, *i.e.*, that are necessary to meet the identity, purity, strength, or composition of the dietary supplement or that are necessary to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.

Requirements to establish specifications to control for contamination are included in final § 111.70(a), (b), (c) and (e). As discussed earlier, the specifications for contaminants in final § 111.70(b) refer to those types of contamination of a component or dietary supplement that may adulterate or that may lead to adulteration that are due to contaminants that may be present in or on the components that you receive, based on the nature of the product, its source, its handling prior to receipt, or other reason. Limits are established by the manufacturer for such contaminants at receipt.

The requirement to establish specifications to control for contamination under final § 111.70(a) and (c) include specifications necessary to prevent adulteration under 402 (a)(1), (a)(2), (a)(3), and (a)(4) of the act as a result of what the manufacturer may do or fail to do in its manufacturing

operation, and not as a result of contaminants that are in or on the components received. For example, it may be critical that a certain piece of equipment be cleaned and/or sanitized after handling certain raw materials to ensure that there is no microbial contamination from microorganisms of public health significance to components processed on the equipment. If the manufacturer failed to establish a specification for cleaning and/or sanitizing after handling those raw materials before processing components, the manufacturer would have failed to establish a specification required by final § 111.70(a) or (c) necessary to prevent a type of contamination that may lead to adulteration under § 402(a)(4) of the act. We would consider it a failure to follow CGMP requirements if a manufacturer allowed conditions in the manufacture of a dietary supplement that would not ensure the quality of the dietary supplement.

We have specified in final § 111.70(b) that you must establish certain types of specifications that are critical to ensuring that you know what the components are that you use in manufacturing a dietary supplement and that are necessary to ensure that the dietary supplements you manufacture meet their specifications for identity, purity, strength, composition, and do not exceed their limits for contaminants. The identity,

purity, strength, and composition, and the limits that you establish for contaminants, for a finished batch of dietary supplement are what we call "product specifications" in final § 111.70(e). These product specifications must be met in order for you to ensure the quality of your finished batch of dietary supplement. A specification may include a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. For example, a specification for a component may include information about the test used to verify the identity of the component and the range of test results that are acceptable. Under final § 111.70(c) a specification for an in-process control may include information about the viscosity that must be achieved during a batch production of a liquid product and information about the test or equipment used to measure the viscosity. Under final § 111.70(d) a specification for packaging may include the specific type or grade of plastic. Under final § 111.70(e) a specification for the finished batch may include the quantitative amount of a dietary ingredient, such as vitamin C.

Under this final rule, the manufacturer has the flexibility -- and the responsibility -- to develop specifications that are

appropriate to the circumstances, including whether information in any particular monograph is an appropriate model for a given dietary supplement.

1. Final § 111.70(a)

Final § 111.70(a) requires you to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record. Final § 111.70(a) derives from the opening statement in proposed § 111.35(e).

As we discussed in the preamble to the 2003 CGMP Proposal(68 FR 12157 at 12196), the points, steps, or stages where specifications must be established may include heating steps, cooling steps, points where specific sanitation procedures are needed, product formulation control steps, points where cross contamination may occur, and steps where employee and environmental hygiene are necessary to ensure the quality of the dietary supplement. These specifications are regulatory specifications addressed by these CGMP regulations. The final rule does not prevent you from establishing additional, nonregulatory specifications that are not at points, steps, or

stages where control is necessary to ensure the quality of the dietary supplement. For example, you could establish specifications that largely address the appearance of the dietary supplement in an aesthetic sense. Such nonregulatory specifications are not addressed by the final rule.

(Comment 161) One comment notes that labelers would not be subject to proposed § 111.35(e).

(Response) Consistent with final § 111.1, persons who perform labeling operations are, in fact, subject to the final rule, including the requirements to establish specifications. As discussed in this section, the final rule includes an explicit requirement that, if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to ensure that the product that you receive is adequately identified and is consistent with your purchase order (final § 111.70(f)).

(Comment 162) One comment asks whether the manufacturer determines where control is "necessary" to prevent adulteration.

(Response) In accordance with the changes made to the section, the manufacturer does determine where control is necessary to ensure the quality of the dietary supplement.

(Comment 163) Some comments express concern that manufacturers who must confirm the validity of subjective criteria established as specifications may set the specifications as low as possible or set meaningless specifications.

(Response) The specifications you must establish under this final rule are designed to ensure the quality of the dietary supplement that you manufacture. It is not meaningless to establish requirements that will ensure, for example, the product meets the established specifications for identity, purity, strength, and composition, and is within specified limits on contaminants to prevent adulteration.

(Comment 164) Some comments express concern that the language of proposed § 111.35(e) may require specifications beyond those already required in the master manufacturing record, as stated in proposed § 111.45(a)(1), to identify specifications for the points, steps, or stages, in the manufacturing process where control is necessary to prevent adulteration, or may require specifications for attributes that are not present at all stages. These comments urge us to be flexible during inspections as to what specifications are appropriate.

(Response) Final § 111.70(a) provides the manufacturer with flexibility in determining what specifications may be necessary

for its operation. Moreover, final § 111.70(a) through (g) provide the manufacturer with flexibility to determine what the specifications require in order to ensure the quality of the dietary supplement.

2. Final § 111.70(b)

Final § 111.70(b) requires you to establish component specifications for each component you use in the manufacture of a dietary supplement. Under final § 111.70(b)(1), you must establish an identity specification for each component that you use in the manufacture of a dietary supplement. A specification for identity may include more than one attribute. For example, a specification for the identity of a salt used in the manufacture of a vitamin and mineral supplement may include the physical characteristics of the solid (e.g., as a crystal or as a powder), the color, and the state of hydration (e.g., with two or three molecules of water). A specification for the identity of a botanical may include the part of the plant (e.g., roots or leaves), the color, and whether the part of the plant is in a native state or has been ground. Under final § 111.70(b)(2), you must establish component specifications that are necessary to ensure that specifications for the purity, strength, and composition of dietary supplements manufactured using the

components are met. Under final § 111.70(b)(3) you must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement. Final § 111.70(b) derives from proposed §§ 111.35(e)(1) and (k). Final § 111.70(b) is consistent with comments, already discussed, that recommended the provisions of proposed § 111.35(k) regarding contaminants that could adulterate a product be incorporated into proposed § 111.35(e). In addition, as discussed above with respect to final § 111.55, final § 111.70(b) provides that the required component specifications you must establish for a dietary supplement include identity, purity, strength, and composition.

(Comment 165) A few comments state it is appropriate and acceptable to establish a requirement for a specification for the identity and purity of components, insofar as such specifications are necessary to ensure that components are not contaminated with substances having public health significance. However, these comments argue that specifications for quality, strength, and composition of components should only be required for the quality, strength, and composition that a component is purported to possess. One comment notes this would provide the same

requirement that is currently established for drug products and processing. Some comments recommend that specifications should be established "as appropriate" or "where control is necessary to assure production of a quality product."

(Response) After considering the comments that questioned the need to establish specifications for the identity, purity, quality, strength, and composition of components, as well as the general comments that led to the overall approach that focuses on building quality into a dietary supplement at every stage of the production and process control system (see discussion in section IV), we are requiring in final § 111.70(b)(1) that you establish an identity specification for components that you use. This identity specification is necessary to ensure that the finished dietary supplement meets its specification for identity, because you could not know what your final product contains if you do not know what you put into it. In addition, final § 111.70(b)(2) requires you to establish those component specifications for purity, strength, and composition that are necessary to ensure that specifications for the purity, strength, and composition of dietary supplements manufactured using the components are met.

Final § 111.70(b)(2) provides flexibility for you to determine which component specifications other than identity are,

or are not, necessary to ensure that the final dietary supplement meets its specifications. For example, it is likely that you will need to establish a specification for the strength of vitamin C added as a component, that you use to make a multivitamin supplement, so that you will know how much vitamin C to add to satisfy the specification for the strength of the vitamin C in the final product. Thus, if you are manufacturing a vitamin C tablet with a strength of 50 milligrams (mg) per tablet, you must determine how much vitamin C, of a given strength, you must add in order to produce tablets that will contain 50 mg, after accounting for the theoretical yield at each step in the manufacturing process. However, you may not need to establish a specification for the strength of the tablet coating agent for that multivitamin supplement, if your final specifications include the amount of the tablet coating agent as part of the specifications for the composition, but not the strength of the multivitamin supplement. In most cases, a specification for the composition of the dietary supplement would be sufficient to ensure that the tablet coating agent is used within the established level.

(Comment 166) A few comments express concern about how to determine certain specifications for botanicals, such as the

strength of peppermint leaf. The comments explain that a specification for strength of peppermint leaf could be based on a number of different attributes. One comment argues that establishing specifications for all dietary ingredients may not contribute to any assurance of product quality and will not protect public health. Some comments assert that "quality, strength, and composition" are subjective with respect to botanical ingredients for which no potency claim is made, and, thus, these attributes should not be included in the rule. Another comment asserts proposed § 111.35(e)(1) goes beyond either food or drug CGMPs and that the composition of approximately 1,200 botanicals used in the industry will be impossible to determine in an economically feasible manner.

(Response) To the extent that these comments assert that this final rule should not require you to establish specifications for the strength and composition of botanical ingredients, we disagree. As explained in response to comment 145, it is fundamental to CGMPs that you know what components are used to manufacture your dietary supplement and to ensure that the finished batch of dietary supplement contains the established identity, purity, strength, and composition. As explained in response to comment 40, this final rule does not require that you

establish specifications for the identity, purity, strength, or composition of the various constituents that are inherently present in a natural product such as a botanical. However, as previously discussed in section VI, depending on what you are manufacturing, the product specifications for the finished batch of a dietary supplement may include a specification, for example, of the strength of a substance that is present in the dietary supplement because it is a constituent of a natural product that you add as a component. For example, you may establish a specification for the amount of vitamin C in a dietary supplement that you manufacture by adding the component rose hips. If this is the case, then the component specifications for the natural product must include a specification for the strength of the constituent (e.g., vitamin C) in whatever amount you determine is necessary to meet the specification for the constituent (vitamin C) in the finished batch of dietary supplement.

(Comment 167) One comment asserts it would be more appropriate for proposed § 111.35(e)(1) to address components "that you purchase" than to address components "that you receive," because customers sometimes provide the ingredient or product to be processed and the customer, rather than the manufacturer, establishes the specifications.

(Response) Final § 111.70(b) (derived from proposed § 111.35(e)(2)) requires that component specifications be established for each component that you use in the manufacture of a dietary supplement. Thus, the firm must establish specifications for the components it uses to manufacture a dietary supplement, regardless of whether it manufactures the components itself or contracts with another firm to manufacture the components. The firm that conducts the manufacturing operations, as explained in section VI, would be responsible for complying with all relevant CGMP requirements in this final rule related to its operations.

(Comment 168) One comment asserts that proposed § 111.35(e)(1) is unnecessary because the requirements for testing to meet the manufacturer's specifications are described elsewhere.

(Response) We disagree. The requirements to establish specifications are distinct from what you must do to determine whether specifications are met. Under the final rule (§ 111,73), you have a responsibility to determine whether the established specifications are met. What criteria you must use in order to determine whether specifications are met are set forth in final § 111.75.

3. Final § 111.70(c)

Final § 111.70(c)(1) requires you, for in-process production, to establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. Final § 111.70(c)(1) derives from proposed § 111.35(e)(2). Final § 111.70(c)(1) includes a nonsubstantive, editorial change that we are making for consistency with other regulations in Part 111. This change is to refer to "in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary" rather than "in-process controls in the master manufacturing record where control is necessary."

We also have added that you must establish in-process specifications, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement. This clarifies that if it is necessary to establish limits on contaminants in-process, due to contamination that may occur in the facility you

do so under final § 111.70(c)(1). With a requirement to set, as necessary, limits on contamination in-process, aspects of the production and process system from receipt to finished product are covered with respect to contamination. For example, under final § 111.70(e) you may determine that you need to establish a microbiological specification that the aerobic plate count of your finished batch of the dietary supplement will not exceed a certain number of colony forming units per gram of product. Under the written instructions in your master manufacturing record (final § 111.210(h)) and your written procedures for manufacturing operations (final § 111.353), you would establish controls to prevent microbial contamination at each point, step or stage in the manufacturing process where control is necessary to prevent microbial contamination. To ensure that you will meet the microbiological specification that you set for the finished batch of the dietary supplement, you may determine that it is necessary to establish a specification for the aerobic plate count at an intermediate stage of the in-process production.

Final § 111.70(c)(2) requires you, for in-process production, to provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the

specifications are met for identity, purity, strength, and composition of the dietary supplements 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 § 111.70(c)(3) requires that quality control personnel review and approve the documentation you provide under final § 111.70(c)(2). Final § 111.70(c)(3) also derives in part from proposed § 111.37(b)(1) which would require the quality control unit to approve or reject all processes that may affect the identity, purity, strength, or composition of a dietary supplement.

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In final § 111.70(c)(2), we are requiring documentation that includes the basis for why meeting the in-process specifications, in combination with meeting the component specifications will help ensure the specifications for the identity, purity, strength, and composition of the dietary supplement and limits on contamination are met. Meeting in-process specifications alone may not ensure the identity, purity, strength or composition of the dietary supplement, but information about the component specification may be needed in order to put the results from the in-process specification in perspective. For example, if the manufacturer establishes a component specification for lead that

it not be greater than “x” mg and establishes a specification that all piping that comes into contact with the component be lead free in the facility, and there are no other components or equipment that would be a source of lead, then there should be no added lead from processing, provided that the material only came in contact with the lead-free pipes and only the other lead-free components and equipment are used. Thus, we would not know by looking solely at the in-process specification whether the lead in the final product is not greater than “x” mg. We would need to evaluate the component specification, in addition to the in-process specification, to ensure that the final product contains no greater than "x" mg lead. To emphasize the interplay of the specifications and component specifications in ensuring the specifications are met for the identity, purity, strength, and composition of dietary supplements, and, as necessary, for limits on contamination, final § 111.70(c)(1) and(c)(2) state “help ensure” rather then “ensure” the identity, purity, strength, and composition of dietary supplements and for limits on contamination.

(Comment 169) One comment asserts monitoring and process controls are more practical and effective than the proposed requirements for in-process testing, which the comment asserts

are overly broad and could impose an undue burden on small businesses.

(Response) The comment's objection is unclear. The final rule requires that you establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary in the manufacturing process to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplement and, as necessary, for limits on contamination. You must monitor the in-process points, steps, or stages, where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met and to detect any deviation or unanticipated occurrence that may result in a failure to meet specifications (see final § 111.75(b)). The final rule does not establish specific requirements for in-process monitoring. The manufacturer must determine any in-process monitoring that is necessary to ensure that the specifications are met for the finished batch. Examples of such monitoring include measuring pH or viscosity.

4. Final § 111.70(d)

Final § 111.70(d) requires you to establish specifications for dietary supplement labels (label specifications) and for

packaging that may come in contact with dietary supplements (packaging specifications). Final § 111.70(d) derives from proposed § 111.35(e)(4). Further, § 111.70(d) requires that packaging that may come into contact with dietary supplements must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the dietary supplements, consistent with proposed § 111.35(e)(4). We deleted the phrase "comply with other statutory and regulatory provisions" from proposed § 111.35(e)(4) because the requirement was redundant with final § 111.5.

5. Final § 111.70(e)

Final § 111.70(e) requires you, for each dietary supplement that you manufacture, to establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement, and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement, all to ensure the quality of the dietary supplement. Final § 111.70(e) derives from proposed § 111.35(e)(3) and (k). Final § 111.70(e) is consistent with comments, already discussed, recommending that the provisions of proposed § 111.35(k) regarding contaminants that could adulterate a product be incorporated into proposed §

111.35(e).

6. Final § 111.70(f)

Final § 111.70(f) requires you, if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), to establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order. Final § 111.70(f) derives from proposed § 111.35(e)(1) which would require, in part, you to establish specifications for dietary supplements that you receive. Final § 111.70(f) includes changes we are making after considering comments.

(Comment 170) One comment notes that labelers would not be subject to proposed § 111.35(e). Other comments request we clarify the roles of the various parties in the "pre-consumer supply chain" for dietary supplements. One comment suggests that manufacturers and packagers be responsible for establishing specifications only for the operations occurring in their own facility or for which they are otherwise responsible (e.g. subcontracted operations), not for upstream or downstream operations over which they may not have any control. This comment states that we intended to relieve packagers from

establishing specifications for the dietary supplements that they package, and also states that such requirements should not be in the CGMP regulations.

(Response) We have discussed, in section VI, who is subject to the final rule under § 111.1 in what the comment describes as the "pre-consumer supply chain" and do not repeat that discussion. We agree that packagers and labelers must establish specifications for the dietary supplements that they package and did not intend to relieve them of complying with relevant CGMP requirements. We recognize that a firm that only packages and labels a product may rely on information about the content of the product that it receives from the manufacturer. The information may consist of an invoice, certificate, guarantee, or other form of verification as to what the product consists of so that the packager or labeler has adequate information about the dietary supplement it receives to label the product and to ensure that the product is consistent with its purchase order. Therefore, we are setting forth certain requirements that distinguish a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) from a product you manufacture. One such requirement is final § 111.70(f) which requires you to establish specifications for a

product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier).

The inclusion of final § 111.70(f), or any other provision that relates explicitly to a product you receive for packaging or labeling as a dietary supplement, does not alter the fact that such a product is no different from any other dietary supplement as far as the applicability of these CGMP requirements.

Under final § 111.70(f), the specifications you establish for a product you receive for packaging or labeling as a dietary supplement must provide sufficient assurance that the received product is adequately identified and is consistent with your purchase order. For example, you may be purchasing tablets that provide 500 mg (strength) (quantitative amount per serving) of vitamin C (identity). Therefore, your purchase order would need to include the identity and amount of vitamin C per tablet to distinguish it from other tablets of vitamin C that may contain only 60 mg, or from other vitamin tablets of 500 mg that you may also purchase.

Final § 111.70(f) sets forth a requirement for a product you receive for packaging or labeling as a dietary supplement that will be distributed by you, rather than returned to the firm from

which you receive the product. Thus, § 111.70(f) applies to product that has left the control of the person who manufactured the batch.

If you are a packager or labeler who packages and labels for the manufacturer and you will return the packaged and labeled dietary supplement to the manufacturer, we would not consider that you are "receiving" product within the meaning of final § 111.70(f). Thus, you would not be subject to final § 111.70(f).

(Comment 171) Some comments assert that "packaging" should be included with "manufacturing process," but that a firm involved only in "holding" a product should not have to set specifications.

(Response) Under final § 111.70(a), a person who holds packaged and labeled dietary supplements for distribution and who does no manufacturing, packaging, or labeling, would be required to establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement. For example, a person may need to establish a specification for the temperature at which the product will be held. However, a person who only holds packaged and labeled dietary supplements for distribution is not

required to establish component specifications (final § 111.70(b)), in-process specifications (final § 111.70(c)), specifications for labels and for packaging (final § 111.70(d)), product specifications (final § 111.70(e)), specifications for product received from a supplier for packaging as a dietary supplement (and for distribution rather than for return to the supplier) (final § 111.70(f)), or specifications for the packaging and labeling of the finished packaged and labeled dietary supplements (final § 111.70(g)) because the person does not engage in any of those activities. This is consistent with the views expressed by the comments regarding the applicability of proposed § 111.35(e) to persons who only hold packaged and labeled dietary supplements for distribution.

7. Final § 111.70(g)

Final § 111.70(g) requires you to establish specifications for the packaging and labeling of the finished packaged and labeled dietary supplements, including specifications that ensure you used the specified packaging and you applied the specified label.

Final § 111.70(g) is a new provision we are adding for clarity and consistency. We had proposed to require that you conduct a material review and make a disposition decision of any

packaged and labeled dietary supplements that do not meet specifications (proposed § 111.70(c)). We proposed minimum standards for packaged and labeled dietary supplements -- i.e., we would require that the quality control unit collect representative samples of each batch of packaged and labeled dietary supplements to determine whether you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record (proposed § 111.37(b)(11)(iv)). Final § 111.70(g) includes the minimum standards that we proposed to establish for packaged and labeled dietary supplements in proposed § 111.37(b)(11)(iv).

To make clear that the use of packaging and labels for a final packaged and labeled product must be that which is specified in the master manufacturing record, we have created a separate provision (under final § 111.70(g)) requiring you to create the relevant specifications to be met.

Final § 111.70(g) requires you to establish specifications that ensure you use the "specified packaging" and to apply the "specified label" as we proposed under proposed § 111.37(b)(11)(iv). We removed the words "specified in the master manufacturing record" as an editorial change that we are making to simplify the language of the requirement.

As already explained (see discussion of final § 111.70(a)), the specifications you establish under final § 111.70 are regulatory specifications required by these final CGMP requirements. The final rule would not prevent you from establishing additional, nonregulatory specifications, such as specifications that largely address the appearance of the dietary supplement in an aesthetic sense.

H. What is Your Responsibility for Determining Whether Established Specifications are Met? (Final § 111.73)

Final § 111.73

Final § 111.73 requires you to determine whether all specifications you establish under final § 111.70 are met. The criteria for determining whether the specifications that you establish under final § 111.70 are met are set forth in final § 111.75. The oversight by quality control personnel for determining whether specifications established under final § 111.70 are met in accordance with the criteria established under final § 111.75 and under what conditions quality control personnel can approve deviations from specifications are set forth in final § 111.77 and final subpart F. Although final §

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111.73 requires you to determine whether specifications are met, it is the responsibility of quality control personnel to conduct a material review and make a disposition decision if a specification established in accordance with final § 111.70 is not met.

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Final § 111.73 derives, in part, from proposed §§ 111.35(f), (g), and (h). Final § 111.73 includes changes associated with reorganization, and other revisions associated with final § 111.70. Final § 111.73 neither includes any finished batch testing requirements that derive from proposed § 111.35(g)(3) nor specifies what you must do to determine whether all specifications are met because the requirements for what means and methods you must use to determine whether specifications are met, including certain requirements for testing, are set forth in final § 111.75.

The comments relevant to final § 111.73 are the general comments that recommend an overall approach that focuses on building quality into a dietary supplement throughout the production and process control system. Because the primary focus of the relevant comments is on the proposed requirements for testing, we discuss those comments when we describe the derivation of the testing requirements in final § 111.75.

I. What Must You Do to Determine Whether Specifications Are Met? (Final § 111.75)

Final § 111.75 derives from proposed §§ 111.35(f),(g),(h), (k), and (l), 111.37(b)(11), and 111.40(a) and (b). Final § 111.75 describes the steps you must take to determine whether specifications are met.

(Comment 172) Many comments assert that the CGMPs for dietary supplements should place greater emphasis on in-process controls and HACCP principles. The comments state FDA's narrow focus on finished product testing is not in line with the philosophy of HACCP, in which manufacturing steps are controlled and verified so as to result in end products that are safe, with minimal finished product testing. One comment cites a 1997 document entitled "Hazard Analysis and Critical Control Point Principles and Application Guidelines" in which we state that "[A]n effective HACCP system requires little end-product testing, since sufficient validated safeguards are built-in early in the process." (Ref. 31).

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(Response) In the 1997 ANPRM, we asked for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be

more effectively addressed by a regulation based on the principles of HACCP, rather than the system outlined in the industry submission (62 FR 5708). HACCP is a science-based, systematic approach to preventing food safety problems by anticipating how such problems are most likely to occur and by installing effective measures to prevent them from occurring. The HACCP concept is a systematic approach to the identification and the assessment of risk (likelihood of occurrence and severity), and control of the biological, chemical, and physical hazards associated with a particular food production process or practice. HACCP is a preventive strategy. It is based on development by the food producer of a plan that anticipates food safety hazards and identifies the points in the production process where a failure would likely result in a hazard being created or allowed to persist; these points are referred to as critical control points (CCPs).

Under HACCP, identified CCPs are systematically monitored, and records kept of that monitoring. Corrective actions are taken when control of a CCP is lost, including proper disposition of the food produced during that period, and these actions are documented. Thus, the focus of a HACCP-based approach is to anticipate food safety hazards, take actions to prevent them, and

keep records of both the actions taken to prevent problems and the actions taken if a problem nonetheless occurs.

As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12174), most of the comments that we received to the ANPRM opposed basing a CGMP regulation for dietary supplements on HACCP principles. Consistent with those comments, we proposed certain requirements that, although consistent with a HACCP-based approach, did not require a HACCP-based approach. For example, proposed § 111.65 would establish requirements for manufacturing operations, including several proposed requirements to prevent contamination of components or dietary supplements, but would not require that you develop a specific plan for the precautions that you would take, or that you keep records of any monitoring that was directed solely at preventing specific types of contamination.

In contrast to the specific focus of HACCP to anticipate food safety hazards, take actions to prevent them, and keep records of both the actions taken to prevent problems and the actions taken if a problem nonetheless occurs, CGMP requires that you take all necessary steps to both prevent hazards and ensure that the product that you manufacture is what you established in your specifications. The proposed testing requirements were

directed at ensuring that a dietary supplement meets all of its established specifications, including specifications for the identity, purity, strength, and composition, rather than on ensuring only that specific food safety hazards that you take steps to prevent are not, in fact, present in the dietary supplement. The comments that assert that the CGMP requirements should place greater emphasis on HACCP principles and, in so doing, reduce the requirements to test product at the finished batch stage, did not explain how the preventive measures that are associated with a HACCP plan would be effective at ensuring that a dietary supplement is what you established it to be in your specifications. Therefore, we are not, as the comments request, including additional HACCP requirements as part of the overall approach set forth in this final rule.

In the 2003 CGMP Proposal, we noted that you may voluntarily choose to implement a HACCP plan that meets the requirements of the National Advisory Committee on Microbiological Criteria for Foods, but that proposed part 111 would still apply to you. (68 FR 12157 at 12174) We also noted that any HACCP plans that are intended to meet the records requirements under proposed part 111 would be treated as records under the CGMP regulations.

(Comment 173) One comment states that it supports a

requirement that a firm ensure that specifications have been met and asserts that the 2003 CGMP Proposal failed to do so. This comment asserts the specific testing requirements in proposed § 111.35(g)(l) and (2) must be significantly modified and suggests that a more effective approach would be to establish separate requirements for ensuring that specifications are met in each of the four categories addressed by proposed § 111.35(e): goods received (§ 111.35(e)(1)); in-process controls (§ 111.35(e)(2)); manufactured goods (§ 111.35(e)(3)); and labels and packaging (§ 111.35(e)(4)).

(Response) The final rule is consistent with this comment. Final § 111.70 requires you to establish certain specifications (including specifications for components, in-process controls, the finished batch and packaging and labels), and final § 111.75 sets forth the requirements for what you must do to determine whether those specifications are met.

1. Final § 111.75(a)

Final § 111.75(a)(1) requires you, before you use a component that is a dietary ingredient, to conduct at least one appropriate test or examination to verify the identity of the dietary ingredient. We recognize, however, that it may be possible for a manufacturer to demonstrate, through various

methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an Interim Final Rule published elsewhere in this FEDERAL REGISTER, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met.

Final § 111.75(a)(2) requires you, before you use a component, to confirm the identity of other components and determine whether other applicable component specifications established in accordance with § 111.70(b) are met. To do so, final § 111.75(a)(2) requires you to either conduct appropriate tests or examinations (final § 111.75(a)(2)(i)); or rely on a certificate of analysis from the suppler of the component that you receive (final § 111.75(a)(2)(ii)). Final § 111.75(a)(2)(ii) sets forth the criteria that you must satisfy in order to rely on

a certificate of analysis from a supplier:

(1) You must first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;

(2) The certificate of analysis must include a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations;

(3) You must maintain documentation of how you qualified the supplier;

(4) You must periodically reconfirm the supplier's certificate of analysis; and

(5) Quality control personnel must review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

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Final § 111.75(a)(1) and (a)(2) derive, in part, from proposed § 111.35(g) and (h) and proposed § 111.40(a)(2) and (a)(3). Final § 111.75(a)(1) and (2) include changes that we are making after considering comments to proposed § 111.35 and proposed § 111.40(a).

(Comment 174) Many comments assert that a certificate of analysis from a properly certified supplier can be a key element

of the manufacturing process, and reduce the need for testing at the finished batch stage. Some comments specifically recommend the dietary supplement manufacturer conduct identity tests to ensure that the correct component has been received. (Also, see Comment 145.)

Some comments recommend an appropriate vendor qualification program, including a combination of vendor audits and product testing, to alleviate the need for complete testing of every lot of incoming components.

Several comments stress that a meaningful certificate of analysis must be based on the results of actual analytical testing. One comment adds that reliance on a supplier's certificate of analysis should be conditioned on a qualification program whereby the recipient independently verifies the supplier's ability to conduct tests and verifies test results through confirmatory testing.

Many comments provide suggestions for ways in which manufacturers could demonstrate the reliability of a certificate of analysis, which include the following: (1) identity testing of ingredients and components; (2) maintenance of documentation of appropriate test results; (3) appropriate verification of the information provided initially and at appropriate intervals; and

(4) documentation that any suppliers have adequate CGMP programs in place.

Some comments recommend that vendor certification programs include plant visits and inspections, while other comments do not believe manufacturers should be required to conduct plant inspections. Other comments recommend that vendor certification programs include CGMP audits or process reviews at supplier facilities; verification of laboratory test results against a certificate of analysis; and 100 percent inspection and testing of incoming materials for a specified period of time while reliability is being assessed.

Some comments provide suggestions for the types of information that should be included on an acceptable certificate of analysis, such as moisture, sieve analysis, identity, and results of tests against established raw material specifications and specifications of any compendia referenced on the label. One comment suggests that a certificate of analysis could be converted into sworn affidavits to guarantee their reliability. Some comments suggest that a system of testing one batch for agreement with the certificate of analysis, and then relying on this information for future purchases, would work well if the suppliers are required to provide reliable and valid certificate

of analysis documents. One comment suggests we issue guidelines as to what should be included in a properly verified certificate of analysis.

Some comments address the requirement in proposed § 111.40(a)(2) to "Visually examine the suppliers invoice, guarantee, or certification * * * and perform testing, as needed, to determine whether specifications are met." One comment agrees with this proposed requirement and asserts that the supplier's certification is not sufficient to ensure that appropriate standards are met. Other comments, however, disagree with this aspect of the proposed requirement or ask for further clarification. A few comments assert that manufacturers should not have to retest material already tested by a supplier. Some comments note that a certificate of analysis can be used for ensuring received materials are consistent with the purchase order, and assert the certificate of analysis can be an appropriate way to ensure specifications are met without requiring testing. One comment suggests the phrase "perform testing, as needed" be replaced with "perform testing, if necessary" and that the CGMP regulations allow for the use of a certificate of analysis that has been verified through a vendor certification process. Another comment states that the

provisions requiring testing in proposed § 111.40(a)(2) are more burdensome than those required of food and pharmaceutical products and cites the drug CGMP provision that permits the use of certificates of analysis in lieu of testing for conformity with written specifications. One comment supports the idea of testing upon receipt in the specific circumstance when testing cannot be performed on the finished product.

Several comments contend that there is a conflict between the 2003 CGMP Proposal and our position during our stakeholder meetings. The comments assert that, at the meetings, FDA representatives recognized that a verified certificate of analysis is acceptable, provided it is based on appropriate testing from suppliers who are audited by their customers as to their testing and manufacturing practices.

A few comments say the 2003 CGMP Proposal should allow more reliance on strict chain of custody and documentation requirements. Other comments recommend that manufacturers not be required to retest previously tested incoming ingredients if they arrive with the vendor’s seal intact. Rather, the purchaser should be able to rely on the vendor’s test results, as presented in a verified certificate of analysis, unless there has been a breach in quality control during distribution and subsequent

manufacture. One comment notes the Canadian regulations for Natural Health Products allow periodic testing of ingredients if a manufacturer has satisfactory evidence that the raw materials sold to him/her are consistently manufactured in compliance with established specifications.

(Response) We agree that CGMP requires that a person who manufactures a dietary supplement conduct at least one appropriate test or examination to verify the identity of each dietary ingredient that will be used in the manufacture of the dietary supplement. For example, because some botanicals require microscopic examination and comparison to a reference to be distinguished, and because suppliers of such botanicals may manufacture several of these botanicals, it is important to verify that a botanical that you receive from a supplier is the correct botanical. In some cases, a single test or examination may be all that is needed to verify the identity of a dietary ingredient; in other cases, it may be necessary to conduct more than one test or examination. It is the responsibility of the manufacturer to determine the appropriate test(s) or examination(s) necessary to verify the identity of a dietary ingredient.

The comments discussed the importance of testing all

components for identity and did not appear to limit their recommendation for conducting identity tests to those components that are dietary ingredients. Based on the comments, we conclude that many firms would conduct an identity test for most ingredients and other components rather than limit identity testing to dietary ingredients. However, because dietary ingredients are the central defining ingredient of a dietary supplement, final § 111.75(a) only requires you to conduct tests or examinations to verify the identity of any component that is a dietary ingredient. As discussed previously in this section, we recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to provide, in an Interim Final Rule published elsewhere in this FEDERAL REGISTER, a procedure that allows for submission to, and review by, FDA of an alternative to the

required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met. For components other than dietary ingredients you must confirm the identity of the component and you have the flexibility of relying on a certificate of analysis, in lieu of conducting a test or examination, to confirm identity. The preamble to the 2003 CGMP Proposal discussed why we were not proposing that you could rely on a certificate of analysis, but did not express a view as to whether the establishment of minimum criteria for how you would qualify the supplier, and for what must be included on the certificate of analysis, could alleviate our concerns about whether the certificate of analysis could ensure certain attributes of dietary supplements.

After considering the comments, we also are persuaded that it is possible to rely on a certificate of analysis from the supplier, for attributes other than identity of the dietary ingredient, provided you satisfy certain minimum criteria set forth in final § 111.75(a)(2)(ii). These criteria include qualifying the supplier, maintaining documentation of how you qualified the supplier, periodically reconfirming the supplier's certificate of analysis, and having quality control personnel review and approve the documentation setting forth the basis for

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qualifying the supplier. These criteria also require that the certificate of analysis, at a minimum, includes a description of the test or examination method(s) used, limits of the tests or examinations, and the actual results of the tests or examinations. Under final § 111.75(a)(2)(ii)(A), to qualify the supplier you must establish the reliability of the supplier's certificate of analysis through confirmation of the supplier's tests or examinations.

Certain comments request that we provide guidance on what should be included in a certificate of analysis. As stated earlier in this section, a certificate of analysis is a document, provided by the supplier of a component prior to or upon receipt of the component, that documents certain characteristics and attributes of the component. Instead of guidance, we are establishing, in final § 111.75(a)(2)(ii)(B), minimum criteria that a certificate of analysis must meet to satisfy these CGMP requirements. As we gain experience in applying the CGMP regulations, we will consider whether it is appropriate to provide guidance on certificates of analysis.

(Comment 175) One comment asks if a raw material contains an unknown amount of excipients, is it necessary to quantify the excipients or can a company simply assess the active material and

rely on a vendor's specification for the excipient content?

(Response) To the extent that this comment is asking whether it is necessary to set a component specification for the strength of excipients that are present in a dietary supplement, the final rule does not require you to do so provided that such a component specification is not necessary to ensure that the specifications for the purity, strength, composition, or contamination limit for the dietary supplement manufactured using the excipients are met (final § 111.70(b)(2)). If such a strength specification for an excipient is necessary to ensure that the purity, strength, or composition specifications are met, or that a contamination limit is met for the dietary supplement, you could, as the comment suggested, rely on a certificate of analysis for that quantitative information provided that you satisfy the criteria set forth in final § 111.75(a).

2. Final § 111.75(b)

Final § 111.75(b) requires that you monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met, and to detect any deviation or unanticipated occurrence that may result in a failure to meet specifications. Final § 111.75(b) derives from

proposed § 111.35(f) with revisions associated with final § 111.70(c)(1).

(Comment 176) A few comments argue that it is not possible to monitor in-process for those specifications required under proposed § 111.35(e). One comment states that a specification such as identity is no longer identifiable at an in-process stage. This comment also notes any such requirement in proposed § 111.35(e) would be redundant, because proposed § 111.35(h) requires a firm to ensure, through testing or examination, that all established specifications are met. Another comment contends that some specifications are not met until processing is complete, such as with liquid extracts. A few comments recommend that the requirement for monitoring be limited to ensuring that specifications established for in-process controls under proposed § 111.35(e)(2) and finished product under proposed § 111.35(e)(3) are met.

One comment states it is not always possible for a manufacturer to monitor for strength and purity of raw materials during in-process steps. The comment suggests this proposed requirement be removed or revised.

(Response) The comments may have misunderstood what we refer to as “in-process” specifications. Under final § 111.75(b), you

must monitor the in-process points, steps or stages where control is necessary to ensure the quality of the finished batch of dietary supplement, to determine whether the in-process specifications are met, and to detect any deviation or occurrence that may result in a failure to meet specifications. The in-process specifications that you establish ensure that, for example, the specification for strength is achieved. If you must deliver a certain amount of powdered Vitamin C to a mixture at a certain point in the process in order to achieve a final product that contains 60 mg of Vitamin C, a critical point in the process is where "x" mg of Vitamin C is added to ensure that the final product contains 60 mg of Vitamin C. You would monitor the operation to ensure that "x" mg of Vitamin C is added. Your strength specification may be tested at the end of the process as a product specification, but your in-process specification to ensure the addition of "x" mg of Vitamin C is a specification that is separate and distinct from the specification that you establish for strength, i.e., 60 mg Vitamin C. You may determine that in-process specifications are met through a test or examination. You could monitor for the vitamin C product by checking the equipment you use to mix the vitamin C-containing product to ensure that the mixing process was carried out during

the time period specified in the master manufacturing record to ensure uniformity in the finished batch. Other examples could include a measurement, such as checking pH during the course of a process, or removing samples during the course of a process to conduct a test for viscosity. There may be no need for certain in-process specifications to ensure that specifications for identity, purity, strength, and composition of the finished batch of dietary supplement are met. If there are no in-process points, steps, or stages at which any test or examination is needed to ensure that the identity specification for the finished batch of dietary supplement is met, then you would not need to establish an in-process specification to ensure identity in the finished batch, and, therefore, would not need to conduct in-process monitoring for identity.

(Comment 177) One comment requests clarification on what would be considered "in-process" for materials that are simply blended together to form a final product. The comment asks how a firm would test the samples if a final material cannot be tested due to interferences or lack of an available method.

(Response) Examples of in-process specifications when materials are simply blended together are the mixing time and speed.

(Comment 178) One comment points out that in-process testing for "unanticipated occurrences" required under proposed § 111.35(f) would be difficult, because the manufacturer would not know what to test for.

(Response) This comment may have misunderstood the provision, which did not propose to require that you test for an unanticipated occurrence. Rather, proposed § 111.35(i)(2) would require you to review the results of any monitoring, and conduct a material review and make a disposition decision, if there is any unanticipated occurrence that adulterates or could result in adulteration of a component or dietary supplement. An example of such an occurrence is leakage of extraneous material from a pipe onto a component. Quality control personnel, under final § 111.113(a)(3), must conduct a material review and make a disposition decision if there is such an unanticipated occurrence during the manufacturing operations.

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(Comment 179) One comment suggests that the provision is a HACCP requirement and is unnecessary for dietary supplements whose production generally does not involve bacterial contamination.

(Response) We disagree. It is not a HACCP requirement because the provisions deal with unanticipated occurrences.

Dietary supplement production can involve bacterial contamination as discussed in section V. The purpose of final § 111.75(b) is to ensure that the product meets all specifications, which include specifications associated with contamination, and, therefore, is a necessary provision.

3. Final § 111.75(c) and (d)

Final § 111.75(c) requires you, for a subset of finished dietary supplement batches, which you identify through a sound statistical sampling plan (or for every finished batch), to verify that your finished batch of the dietary supplement meets product specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the dietary supplement. Final § 111.75(c) also sets forth the following verification requirements:

(1) You must select one or more established specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batch of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product

specifications (or only those product specifications not otherwise exempted from this provision by quality control personnel under final § 111.75(d));

(2) You must conduct appropriate tests or examinations on the specifications selected in final § 111.75(c)(1);

(3) You must provide adequate documentation of your basis for why meeting the specification(s) selected under final § 111.75(c)(1), through the use of appropriate tests or examinations conducted under final § 111.75(c)(2), will ensure that your finished batch of the dietary supplement meets all product specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate, or that may lead to the adulteration of, the dietary supplement; and

(4) Quality control personnel must review and approve the documentation that you provide under final § 111.75(c)(3).

Final § 111.75(c) requires you to verify that your finished batch of dietary supplement meets specifications for identity, purity, strength, composition, and limits that you established for those types of contamination that may adulterate or that may lead to adulteration of the finished batch. You may verify this by either testing or examining (1) every finished batch for each

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of these specifications, or (2) a subset of finished batches for the dietary supplement. The subset of batches tested must be identified using a sound statistical sampling plan.

If you choose to test or examine a subset of finished batches of dietary supplement, you may test or examine each subset of batches for identity, purity, strength, composition and limits on contamination that you established. Alternatively, you may determine that you can select one, two, or three, or other number of these specifications that, if determined to be in compliance with specifications, would be able to verify that the other untested specifications are met. For example, you may be able to substantiate that, if you determine compliance with the specification for the identity and composition of a product for which no contamination limits are needed, the system is adequately controlling for the purity and strength of the product, without the need to test for compliance with the specifications for purity and strength. If so, you must document, under final § 111.75(c)(3) your basis for why this is so. Quality control personnel must review and approve such documentation under final § 111.75(c)(4).

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Under final § 111.75(d), you may determine, in the above example, that you could not verify, by testing for compliance

with the specifications for identity and composition, that the purity specification is met, and there may be no scientifically valid method for testing or examining the finished batch to evaluate the purity in the finished batch of dietary supplement. In that case, you could exempt the specification for purity from the requirement in final § 111.75(c)(1) if you can document why the purity specification is met without such testing or examination. You could do so through, for example, documentation that meeting component and specifications for strength is sufficient, or through documentation that in-process monitoring is sufficient. Quality control personnel must review and approve such documentation (final § 111.75(d)).

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Final § 111.75(c) and (d) derive from proposed § 111.35(g) and (h) and include changes that we are making after considering comments.

(Comment 180) Several comments assert that a more appropriate balance is needed between an effective process control system and a reasonable testing scheme calculated to confirm the quality of dietary supplements. The comments stress it is important to build quality into a product throughout the entire production process by relying on strong process controls rather than by testing at the finished batch stage. One comment

asserts that in an appropriate process control system, testing is a means to monitor and ensure that the control system is functioning as intended. Several comments make a specific recommendation that the final rule include rigorous controls.

Some comments support the requirement under proposed § 111.35(g) to test each batch of finished product when possible, and to perform testing of components and in-process when testing the finished product is not possible. Other comments object to the proposed requirements for finished product testing on the grounds that they are overly burdensome, duplicative, and unnecessary.

Some comments suggest that a more practical approach to finished product testing would be to conduct identity testing of each component, combined with certification of the vendor by a program of complete testing for conformance with a certificate of analysis, as is allowed under the drug CGMP regulations. Some comments suggest manufacturers that have written procedures for each stage of their process, including raw material certification, production, and finished product analysis, and a written plan for qualifying the process, should be exempt from the proposed requirements to test each finished batch. Some comments urge us to give companies the flexibility to devise

testing procedures.

(Response) The approach in final § 111.75(c) and (d) is consistent with these comments and is part of the overall approach of this final rule, which focuses on ensuring the quality of the dietary supplement throughout the production and process control system.

The concept behind final § 111.75(c) and (d) is analogous to the overall concept of proposed § 111.35(g). Under proposed § 111.35(g) you could rely on a combination of meeting component specifications and in-process specifications when you are unable to test for a specification, provided you satisfied certain criteria. Under the final rule, you may rely on a combination of meeting component specifications and in-process specifications to verify that your product meets specifications, rather than test every batch to determine whether specifications are met, regardless of whether a test is available, provided you satisfy certain criteria. Thus, the final rule provides flexibility that is needed to build adequate controls early in the process to reduce the need for end product testing on every batch of finished dietary supplement.

(Comment 181) One comment expresses concern that the requirement to use appropriate tests to determine compliance with

specifications could be interpreted as requiring companies to test dietary supplements not only for compliance with company specifications, but also for compliance with any labeled specifications of the ingredient suppliers, such as for contaminants. The comment believes this would be redundant and overly burdensome.

(Response) As explained in section XXIV, we have made changes to reduce the testing burden on companies while still requiring steps necessary to ensure the quality of dietary supplements. For example, under final § 111.75(a), instead of testing (other than for identity of the dietary ingredients), firms may rely upon supplier certificates of analysis in certain circumstances. Also, we recognize, however, that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would provide no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided

to provide, in an Interim Final Rule published elsewhere in this FEDERAL REGISTER, a procedure that allows for submission to, and review by, FDA of an alternative to the required 100 percent identity testing of components that are dietary ingredients, provided certain conditions are met. In addition, under final § 111.75(c), testing or examination for a portion of the finished batches is an option, and exemptions are provided for in final § 111.75(d).

(Comment 182) One comment points out that, if a product cannot be tested for technical reasons at the final product stage, then it also cannot be tested at the final blending stage in the process, because the nature and composition of the product at both stages are virtually the same. Another comment asks whether a verification of content in the final product will suffice if there is no valid testing procedure.

(Response) Under final § 111.75(c), you have flexibility to select one or more established specifications for identity, purity, strength, composition, and limits on those types of contamination that may adulterate or that may lead to adulteration of the dietary supplement that, if tested or examined on the finished batch of the dietary supplement, would verify that the production and process control system is

producing a dietary supplement that meets all product specifications. Under final § 111.75(d), you have flexibility to exempt one or more product specifications from verification requirements, provided that you satisfy the criteria established under final § 111.75(d).

(Comment 183) Some comments request that the rule include requirements for dissolution, disintegration, and bioavailability testing for dietary supplements. These comments note that, although a product may contain the labeled amount, it may not dissolve readily in the body or be available for absorption.

(Response) We decline to revise the rule as suggested by the comments. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12163), tests for dissolution, disintegration, and bioavailability of dietary supplements are examples of areas where scientific study is still evolving; thus it is premature to impose requirements for such tests. The comments provide no specific information that would alter this view or support the technical feasibility of conducting such tests for all types of dietary supplement products. However, nothing in this final rule would preclude a manufacturer from establishing such requirements. A manufacturer should have data to support any specifications it establishes for parameters such

as dissolution, disintegration, and bioavailability.

(Comment 184) One comment questions the requirements in the 2003 CGMP Proposal that all manufacturers quantify certain marker compounds in their products. The comment offers two reasons why such testing should not be required for botanical products: their food-like composition and legal status; and the assertion that scientifically valid analytical methods may prove to be irrelevant or even hinder the development of superior products.

(Response) The final rule does not require any specific testing requirements, such as testing for marker compounds. You would determine the specific testing requirements, and whether to use a marker compound in those tests, depending on your product and process. In the 2003 CGMP Proposal (68 FR 12157 at 12172), we merely discussed how a marker compound could help you identify whether you have a particular species of an herb to differentiate, for example, between a poisonous and nonpoisonous species.

4. Final § 111.75(e)

Final § 111.75(e) requires you, before you package or label a product you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), to visually examine the product and have documentation

to determine whether the specifications that you established under final § 111.70 (f) are met. Final § 111.75(e) derives from proposed § 111.35(e)(1) and (g) and from proposed § 111.40(a)(2).

(Comment 185) Some comments request we clarify the roles and testing obligations of the various parties in the "pre-consumer supply chain" for dietary supplements. Some comments argue that redundant tests should not be required at every transaction point in the pre-consumer supply chain. The comments contend that any testing already performed by a supplier, manufacturer, or packager should suffice, so long as other CGMP certification, and chain of custody standards, are met. Other comments urge us to give companies the flexibility to devise testing procedures and point out that different testing is needed for different roles in the supply chain.

One comment requests clarification of the testing requirements applicable to packagers/labelers. The comment states it is unclear how a packager or labeler/distributor could conduct testing of component ingredients if all the firm receives is a finished product for which there is no scientifically valid testing method.

(Response) As discussed in section VI, you are responsible for the CGMP requirements that are applicable to your operations.

We agree that redundant tests should not be required. Further, we agree that it is the responsibility of the manufacturer to do component testing. The packager or labeler does not need to do any required component testing because the packager or labeler does not receive components, rather it receives a finished dietary supplement. Under final § 111.70(f) if you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order.

Under final § 111.75(e), before you package or label such a product, you must visually examine the product and have documentation to determine whether the specifications that you established under final § 111.70(f) are met. Your documentation may consist of an invoice, certificate, guarantee, or other documentation from the supplier to ensure that the product is adequately identified and is the product that you ordered. Final § 111.75(e) does not require that the documentation consist of the result of testing or examination by the packager or labeler of such a product.

As with final § 111.70(f), final § 111.75(e) applies to

"product that you receive for *** for distribution rather than for return to the supplier" and, thus, applies to product that has left the control of the person who manufactured the batch. If you are a packager or labeler who packages and labels a dietary supplement for the manufacturer, and you will return the packaged and labeled dietary supplement to the manufacturer, we would not consider that you are "receiving" product within the meaning of final § 111.75(e). Thus, you would not be subject to final § 111.70(f).

5. Final § 111.75(f)

Before you use packaging, final § 111.75(f)(1) requires you, at a minimum, to conduct a visual identification of the containers and closures and review the supplier's invoice, guarantee, or certification to determine whether packaging specifications are met. Before you use labels, final § 111.75(f)(2) requires you, at a minimum, to conduct a visual examination of the label and review the supplier's invoice, guarantee, or certification to determine whether labeling specifications are met. Final § 111.75(f)(1) and (2) derive from proposed § 111.40(b)(2) which, in part, would require you, for packaging and labels you receive, to conduct at least a visual identification on the containers and closures. Proposed §

111.40(b)(2) also would require you, in part, for packaging and labels you receive, to quarantine the packaging and labels until your quality control unit tests or examines a representative sample to determine whether specifications are met. Consistent with changes that we are making to the requirements for packaging and labels that you receive (see discussion of final § 111.160 in section XII), final § 111.75(f)(1) and (f)(2) include a requirement analogous to proposed § 111.40(a)(2) which would require you to visually examine the supplier's invoice, guarantee, or certification to determine whether the components, dietary ingredients, or dietary supplements you receive are consistent with your purchase order and to perform testing, as needed, to determine whether specifications are met.

6. Final § 111.75(g)

Final § 111.75(g) requires you, at a minimum, to conduct a visual examination of the packaging and labeling of the finished packaged and labeled dietary supplements to determine whether you used the specified packaging and applied the specified label. Final § 111.75(g) derives from proposed § 111.37(b)(11)(iv) which would require the quality control unit to collect representative samples of each batch of packaged and labeled dietary ingredients or dietary supplements to determine whether you used the

packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record. Final § 111.75(g) is associated with final § 111.70(g) which requires you to establish specifications for the packaging and labeling for the finished packaged and labeled dietary supplements, including specifications that ensure you used the specified packaging and applied the specified label.

7. Final § 111.75(h)

Final § 111.75(h)(1) requires you to ensure that the tests and examinations you use to determine whether the specifications are met are appropriate and scientifically valid methods. Final § 111.75(h)(1) derives from proposed § 111.35(h). Final § 111.75(h)(1) includes editorial changes associated with the reorganization and changes that we are making after considering comments.

Final § 111.75(h)(2) requires that the tests and examinations you use include at least one of the following: (i) gross organoleptic analysis; (ii) macroscopic analysis; (iii) microscopic analysis; (iv) chemical analysis; or (v) other scientifically valid methods. Final § 111.75(h)(2) derives from proposed § 111.35(l).

(Comment 186) Some comments suggest that the tests listed

in proposed § 111.35(l) be incorporated into proposed § 111.35 (h), relating to appropriate test methods.

(Response) We agree with the comment, and final § 111.75(h)(2) combines these requirements as requested.

(Comment 187) One comment states that the list of tests should be deleted because it is not sufficient to cover the types of testing that will be required for compliance with proposed § 111.35(g).

(Response) The comment does not identify the types of tests that would not be covered. We believe that final § 111.75(h)(2)(v)'s "catch-all" provision, which requires that one of the tests that you use be an "other scientifically valid method" is sufficient to cover all other types of testing required under this final rule.

(Comment 188) One comment states that the final rule should make clear that organolepsis is an acceptable method for identity testing. The comment contends it is imperative for the survival of small businesses that organolepsis be allowed, coupled as necessary with macroscopic and morphological examination and comparison with voucher specimens or photographs. Another comment requests clarification of whether gross organoleptic analysis alone can be a test for releasing finished products. Some

comments assert that several organizations have published relevant methods that include macroscopic methods that can be used in identifying herbal ingredients.

(Response) Organolpetic analysis would be an acceptable method under the 2003 CGMP Proposal and remains an acceptable method under the final rule, which clarifies that the method you use, including organoleptic analysis, must be appropriate. Organoleptic analysis may not be an appropriate method of testing for certain substances. This is particularly true when the nature of the substance decreases the reliability of organoleptic analysis. For example, while organoleptic analysis may be an appropriate identity test for whole or coarsely-cut botanical parts, it may not be an appropriate identity test for powdered or extracted botanicals because of decreased reliability, or in those instances where misidentification of botanicals is known to occur. Additionally, we recognize "macroscopic analysis" is one of the tests or examinations you may select to determine whether specifications are met.

(Comment 189) One comment remarks that the appropriateness of the test depends on the material being tested, and the method selected by the manufacturer may be inappropriate. One comment believes the methods stated in proposed § 111.35(l)

(organoleptic, microscopy, chemical) for establishment of identity and purity would not be applicable to animal products. This comment suggests that a separate list of test methods should be identified for those materials.

(Response) We agree that the appropriateness of the test depends on the material being tested. However, we are not revising the rule to identify methods that are, or are not, appropriate for specific circumstances (such as the case of animal-derived ingredients). There are so many distinct circumstances that such a list would be neither practical nor useful. Beyond that, the manufacturer is responsible for choosing the appropriate test.

(Comment 190) One comment asks us to clarify in the final rule the requirement that methods be scientifically valid applies only to quantitative methods.

(Response) In proposed § 111.35(h), we did not intend that the proposed requirement that you use scientifically valid methods apply only to quantitative methods, because we also proposed that tests in accordance with proposed § 111.35 must include at least one of the following: (1) Gross organoleptic analysis; (2) microscopic analysis; (3) chemical analysis; or (4) other appropriate test. To clarify that the requirement that

methods be scientifically valid applies to all the tests and examinations you use, rather than to quantitative tests alone, final § 111.75(h)(1) does not use the term "analytical."

(Comment 191) One comment states that the proposed definition of "appropriate test" (i.e., "a scientifically valid analytical method") is extremely onerous and violates Congressional intent. The comment believes that mandating specific methods is inappropriate, and dietary supplement CGMPs should comply with E.O. 12866 and not impose additional requirements on small businesses that are better left to normal business practices.

Several comments take issue with our statement that we were not aware of a situation where an appropriate scientifically valid method is not available when, in fact, valid test methods are not always available for testing dietary ingredients or dietary supplements. One comment contends the 2003 CGMP Proposal contains conflicting information about available test methods. For example, the preamble to the 2003 CGMP Proposal states that we are "not aware of a situation where an appropriate scientifically valid analytical method is not available," and our cost analysis does not address costs of method development. At the same time, however, we set out alternatives to finished

product testing in cases where adequate methods are unavailable, and we decline to require expiration dating because there may not be adequate methods available for assessing the strength of a dietary ingredient. The comment cites numerous ongoing efforts in methods development by both industry and government that illustrate the lack of existing methods necessary to confirm compliance with all quality specifications.

(Response) These comments appear to take our statements out of context. In the 2003 CGMP Proposal, we stated: "If an AOAC or FDA method is not available, a scientifically valid analytical method is one that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research. Although there may not be an Association of Official Analytical Chemist (AOAC) or FDA method available, we are not aware of a situation where an appropriate scientifically valid analytical method is not available" (68 FR 12157 at 12198). We also stated: "We recognize that certain tests for identity, purity, quality, strength, or composition for certain finished product may not be available due to complex finished matrices that would make such testing impracticable" (68 FR 12157 at 12197). We disagree that our statement acknowledging that the available tests may not be practicable in certain

matrices is inherently inconsistent with our statement that we are not aware of a situation where an appropriate scientifically valid analytical method is not available. One statement relates to the availability of methods, the other relates to the practicality of using an available method in particular circumstances.

In any case, under final § 111.75(d)(1) you may exempt a product specification from the verification requirements of final § 111.75(c)(1) if you show that: (1) the specifications selected to verify that the product meets all product specifications are not able to verify that the control system is producing a dietary supplement that meets the exempted product specification and (2) there is no scientifically valid method for testing or examining the exempted product specification at the finished batch stage. Section 111.75(c)(1) also requires you to document why other information, such as component and in-process testing, will determine whether the exempted product specification is met without finished batch testing. Although we agree that there may be some circumstances where there is not a scientifically valid method available for finished product testing, we believe that there would be some scientifically valid method available for component or in-process testing.

(Comment 192) One comment encourages flexibility toward the development of a quality system that is based on a balance of prevention, appraisal, and process verification activities. Another comment asks whether the industry should use industry standards and tests now used.

A few comments request that we clarify proposed § 111.35(h) to make it clear whether the section recommends or requires the use of available USP, AOAC or FDA methods. One comment recommends that the final rule give companies flexibility to use the method(s) most suitable to the ingredient they are testing and the specification they have set. The comment adds that companies should then be required to ensure, through appropriate rationale and data, that the method is indeed suitable and produces accurate and reproducible results.

(Response) We agree that companies should have the flexibility to adopt the method most suitable to the ingredient they are testing. As discussed in the preamble to the proposal (68 FR 12157 at 12163, 12208), official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions and the AOAC International methods are often cited as "official validated methods." Other method validations are conducted in a single

laboratory by repeating the same test multiple times. In the case of methods used to support specific regulatory applications to FDA, data and information about methods that are developed and conducted in a single laboratory by repeating the test multiple times are sent to us, together with appropriate samples and reference materials so the test can be repeated in an agency laboratory. Typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness.

The process of method validation discussed above is a formal process for demonstrating that procedures are suitable for their 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 American Herbal Pharmacopoeia 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 (FAC)(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.

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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, 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 this subpart 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

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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).

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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

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compliance with the requirements of final § 111.123(b) (discussed in section XI).

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

- § 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;
- § 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.
- § 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.
- § 111.35(i)(4)(i) which would require, for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary supplement, packaging, or label, you 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.
- § 111.35(i)(4)(ii) which would require, for any deviation or unanticipated occurrence which resulted in or could lead to

adulteration of the component, dietary supplement, packaging, or label, you 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

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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.

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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.

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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 (i.e., AOAC 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 four or five 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)(ll)(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), 111.40(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.

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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 (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, 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 one 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, section XXI.

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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 three 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 one 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.

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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

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decisions. Final § 111.87 derives from a number of proposed requirements for conducting a material review and making a disposition (§§ 111.35(i), 111.35(n), 111.37(b)(5), 111.37(b)(14), 111.40(a)(3), 111.50(d)(1), 111.85(a), and 111.85(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), 111.85(a), and 111.85(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

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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

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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.

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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

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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), (ii) and (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.

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(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, 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 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

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quality control personnel have the responsibility to conduct a material review and make disposition decisions. Thus, we are retaining the requirements in proposed §§ 111.25(i)(4)(ii) and 111.50(d)(1) in final § 111.90(a).

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3. Final § 111.90(b)

Final § 111.90(b) requires that you must not reprocess any dietary supplement, treat or provide and 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.

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(Comment 208) As discussed in section VI (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.

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(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, 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 § 111.23(b) before releasing for distribution. Final § 111.90(c) derives from proposed § 111.50(g).

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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 § 111.23(b) before releasing for distribution. We revised this provision to be consistent with the changes in final § 111.77 and final § 111.23(b).

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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.

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

1. § 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) 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 two 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.

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2. § 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 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 subparagraph (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

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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 this subpart.