

the dietary supplement. In this example, you would be required to establish a purity specification for the amount of triglycerides in the fish oil. (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.) We do, however, expect you to set appropriate limits on contaminants (e.g., toxic substances) that are known to be constituents of botanical extracts or other natural products that are likely or certain to contain constituents that are harmful.

c. *Strength.* The strength of a dietary supplement relates to its concentration. By concentration, we mean the quantitative amount per serving (for example, weight/weight, weight/volume, or volume/volume). Therefore, for purposes of this final rule, strength does not refer simply to the quantity of an ingredient, rather it refers to the amount of a stated ingredient per a specified unit of measure.

If the comments were concerned that the “strength” of a dietary supplement meant that you need to establish the quantitative amount per unit of measure of each constituent in a dietary ingredient, such as a botanical extract or natural product, we do not consider such constituents to be “components” of a dietary supplement, unless you add such constituents as components (as in an extract) (see discussion of the definition of component in this section).

We do not consider the rule’s requirements on dietary supplement strength as necessarily relating to the individual constituents of such products. Whether the requirements regarding dietary supplement strength apply to one or more

constituents of dietary ingredients in a dietary supplement depends on what you are manufacturing. For example, if you are manufacturing vitamin C, and your source of vitamin C is rosehips, you would establish a strength specification for vitamin C in the finished batch of the dietary supplement (e.g., “x milligrams (mg) of vitamin C per tablet”). You are required to ensure that the dietary supplement does in fact contain “x mg of vitamin C per tablet.” Alternatively, if you are manufacturing rosehips and not vitamin C from rosehips, the strength specification that you establish for the finished batch of the dietary supplement is the strength of the rosehips themselves (i.e., the concentration of rosehips in the final product, such as “x mg of rosehips per tablet”). You are required to ensure that the product does in fact contain “x mg of rosehips per tablet.”

We discuss the requirements to establish and meet specifications in our discussion of subpart E (see section X of this document).

d. *Composition.* A dietary supplement’s “composition” refers to the specified mix of product and product-related substances in a dietary supplement. For example, a dietary supplement manufactured to provide vitamin C may contain, in addition to vitamin C, a tablet coating agent and substances used as binders. The composition could be described as the percent of the dietary supplement that is vitamin C, the tablet-coating agent, and each binder.

e. *Other terms.*

(Comment 58) Several comments would revise the rule to define “manufacturer.” Many comments ask whether the rule applies to certain types of companies or professionals and said a definition of “manufacturer” would clarify the rule’s applicability.

Some comments suggest specific text for a definition. For example, one comment would define “manufacturer” as “a person who formulates or changes the composition or physical characteristics of a dietary supplement or who packages or labels the product in a container for distribution” to clarify that a company that does not manufacture a specific dietary supplement, but purchases a dietary supplement in bulk and then packages or labels the bulk dietary supplement for sale to consumers, is still subject to dietary supplement CGMP requirements. The comment cites our proposed definition of “manufacturer” in our infant formula CGMP proposal (see 61 FR 36154 at 36209, July 9, 1996 (proposing to define a “manufacturer” as “a person who prepares, re-constitutes or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution”)).

Other comments would define “manufacturer” to exclude a health care practitioner or herbalist and noted the Canadian Natural Health Product regulations do not apply to health care practitioners.

(Response) We decline to define “manufacturer” in the final rule. In section III, footnote 1 of this document, we explain that “manufacture” is a broad term and is not limited to production, packaging, or labeling activities. Consequently, we prefer to explain our interpretation of the final rule in this preamble and to have the codified provisions state general principles rather than attempt to capture subtleties in a definition of “manufacturer.”

(Comment 59) Proposed § 111.35(e)(1) through (e)(3) would require you to establish specifications for identity, purity, quality, strength, and composition at receipt, in-process, and finished batch stages, while proposed § 111.35(g)(1) would require you to test each dietary supplement at the finished

batch stage before release for distribution to confirm that specifications are met, provided that there are scientifically valid analytical methods available to perform such testing. If your quality control unit determined that finished batch testing could not be completed for any specification because a scientifically valid analytical method was not available, proposed § 111.35(g)(2) and (g)(3) would require you to perform testing on components and at the in-process stage to determine whether that specification is met. The preamble to the 2003 CGMP Proposal explained that 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 (68 FR 12157 at 12198).

Several comments agree that scientifically valid analytical methods are those that are based on scientific data or results published in scientific journals, references, textbooks, or proprietary research. However, several comments ask us to define or better explain the terms “test” or “scientifically valid analytical method” as used in the dietary supplement CGMP final rule. One comment argues that, because of the evolving nature of methodology for ingredients used in dietary supplements, we should give the industry more guidance as to what can be considered authoritative for the purpose of compliance with CGMP. Some comments state we should acknowledge methods from the Institute for Nutraceutical Advancement (INA), American Herbal Pharmacopoeia (AHP), European Pharmacopoeia, and the World Health Organization (WHO) as scientifically valid analytical methods. One comment notes the USP establishes scientifically valid procedures in its compendia and encouraged us to designate compendial procedures as “scientifically valid” by defining “scientifically valid” to include compendial procedures. The

comment further argues that failure to acknowledge compendial procedures as scientifically valid would be inconsistent with section 403(s)(2)(D) of the act, which acknowledges the role of compendia, by considering a dietary supplement misbranded if the supplement is covered by the specifications of an official compendium, is represented as conforming to the specifications of an official compendium, and fails to so conform.

Other comments would define “validation” and “verification” and directed us to “ANSI Standard A8402–1994” (a description of validation and verification standards).

(Response) We decline to define “test,” “scientifically valid analytical method,” or “scientifically valid method” in this final rule. As the comments recognized, the analytical methods for components are evolving. A regulatory definition for “test,” “scientifically valid analytical method,” or “scientifically valid method” could become obsolete if we based it on specific sources such as INA, AHP, or USP that may or may not themselves stay current or that may be modified in a manner that did not enjoy widespread support.

The preamble to the 2003 CGMP Proposal acknowledged that compendia can have a role in establishing tests used to determine whether specifications are met. For example, we noted that compendial standards may be appropriate reference materials for use in conducting tests or examinations (68 FR 12157 at 12208). However, we did not list specific compendia that would be suitable sources or scientifically valid analytical tests, and are not listing such compendia in this final rule. The compendia identified in the comments, i.e., INA, ANSI, AHP, and USP, may include some methods that are based on scientific data or results published in scientific journals, references, textbooks, or proprietary research, but also contain some methods that are not based on

such data or results. Thus, whether or not a method is scientifically valid is not determined solely by its inclusion in a compendium. Rather, it is the responsibility of quality control personnel to approve the use of those scientifically valid tests that will ensure a product's identity, purity, strength, and composition whether or not such tests are contained in a particular compendium.

We also decline to define "validation" and "verification" because the final rule does not establish any requirements that use these terms.

(Comment 60) One comment asks us to define the terms "adequate," "sufficient," and "qualified" and argues that, without these definitions, an FDA investigator may assert that something or someone is not adequate, sufficient, or qualified.

(Response) We decline to define "adequate," "sufficient," or "qualified" in this final rule. Deciding what is "adequate" or "sufficient," or who is "qualified" must be done on a case-by-case basis, depending on the operations and the particular facts. As explained in section V of this document, we do not need to, nor could we, predict with mathematical precision how many inches or feet, for example, would be "adequate space" to allow for cleaning a particular piece of equipment that could be applied to every size of facility and every operation. Furthermore, defining "adequate," as defined in part 110, as "that which is needed to accomplish the intended purpose in keeping with good public health practice" would still require context to determine whether, in a particular operation and based on a particular set of facts the particular practice was "adequate." Moreover, for terms such as "adequate," "sufficient," and "qualified," where there has been common usage in the food industry to enable manufacturers and FDA investigators to comprehend and apply such

terms to a particular operation, we do not believe a definition for these terms is necessary.

(Comment 61) Several comments would define the terms “certificate of analysis,” “certificate of compliance/conformance,” and “continuing product guarantee.” Most comments include these terms in a list of terms that they want us to define to ensure consistent interpretation of the rule throughout the industry. One comment says a standard for documentation, such as a certificate of analysis, would put greater emphasis on the firm’s responsibility to comply with CGMP.

(Response) We decline to define these terms as suggested by the comments. We have included, in the codified, the use of a certificate of analysis as an option to determine whether certain specifications have been met. The final § 111.75(a)(2)(ii)(B) requires that certain information be provided in a “certificate of analysis.” This provision states that 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, provided you satisfy certain other criteria.

As for the claim that a standard for documentation, such as a certificate of analysis, would emphasize a firm’s responsibility to comply with CGMP, we encourage firms who are excepted from the scope of the rule in final § 111.1 and who supply dietary ingredients and other components to follow dietary supplement CGMP requirements.

We decline to define “certificate of compliance/conformance” or “continuing product guarantee” because the final rule does not establish any requirements that use these terms.

## 26. What Definitions Did the Comments Want Us to Delete?

(Comment 62) Some comments would delete certain definitions (e.g., “component” and “ingredient”) because these terms do not appear in the food CGMP, the 1997 ANPRM, or both.

(Response) We decline to delete any definition for the reasons stated by the comments. As discussed in section V of this document, Congress did not require dietary supplement CGMP requirements to be identical to the food CGMP requirements, so the mere fact that a definition may not appear in a food CGMP regulation does not mean we must delete that definition from this final rule, especially when the comments offered no other justification for deleting the definition. Definitions provide clarity and consistency in interpreting various terms in a rule.

### *D. Do Other Statutory Provisions and Regulations Apply? (Final § 111.5)*

Final § 111.5 states: “In addition to this part, you must comply with other applicable statutory provisions and regulations under the act related to dietary supplements.” Proposed § 111.5 stated that, in addition to the dietary supplement CGMP requirements, “you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging or holding of dietary ingredients or dietary supplements.”

Section 111.5 reminds you that other statutory or regulatory requirements, not included in the dietary supplement CGMP requirements, may apply to your particular products, operations, or activities. In our further review of this provision, we determined that we do not need to elaborate on the individual operations and have shortened the provision to eliminate the references to particular operations. You are required to comply with other applicable statutory and regulatory requirements, and we have retained this provision to

ensure you understand that this final rule does not relieve you of your responsibilities to comply with other applicable statutory and regulatory requirements related to dietary supplements.

*E. What Sections Did We Remove From the Rule, and Why?*

The final rule omits sections that were in the proposed rule. Proposed § 111.2, “What Are These Regulations Intended to Accomplish,” would have described the rule’s purpose as establishing the minimum CGMP you must use to the extent that you manufacture, package, or hold a dietary supplement. Proposed § 111.6, “Exclusions,” would have excluded “persons engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary supplement by other persons” from the dietary supplement CGMP requirements.

1. “What Are These Regulations Intended to Accomplish?” (Proposed § 111.2)

We elected to remove proposed § 111.2 from the final rule because we realized that it created no enforceable obligations and provided little, if any, helpful information. The few comments that address proposed § 111.2 either disagreed with its general statement or sought to weaken the provision; the comments’ arguments prompted us to reconsider whether proposed § 111.2 was necessary at all, and, in the end, we decided to delete the proposed section. We describe the comments on proposed § 111.2 in the following paragraphs.

(Comment 63) Several comments argue the proposed rule went beyond the “minimum standards” mentioned in proposed § 111.2. These comments also assert the proposed rule lacked flexibility.

(Response) We disagree with the comments. In several instances, the proposed requirement is practically identical to requirements in the umbrella

food CGMP regulations. For example, most of the proposed requirements for personnel, physical plants, and equipment and utensils correspond to long-established, similar requirements in the umbrella food CGMP regulations in part 110. In other instances, the proposed rule would require a particular action or result (such as establishing specifications for components, in-process controls, manufactured dietary supplements, and packaged and labeled dietary supplements under proposed § 111.35(e)), but gave firms the flexibility and the responsibility to decide what those specifications will be. We have included flexibility where it is appropriate to do so, and, after we revised parts of the rule in response to the comments, the final rule provides more flexibility than the proposal. For example, final § 111.75 sets forth criteria for relying on a certificate of analysis to ensure that certain specifications for components are met and for when you can test a subset of finished batches for a select number of specifications; this differs considerably from the proposal which would have required testing all batches for all specifications.

(Comment 64) One comment would revise proposed § 111.2 to read as follows: “These regulations recommend general minimum current good manufacturing practices that, when modified by manufacturer product specifications, will extend to the manufacture, package, or holding of dietary ingredients or dietary supplements for that manufacturer.”

(Response) We decline to revise the rule as suggested by the comment. Section 402(g) of the act states that “The Secretary may by regulation prescribe good manufacturing practices for dietary supplements.” If a dietary supplement has been prepared, packaged, labeled, or held under conditions that do not meet the final rule’s requirements, the dietary supplement is deemed to be adulterated under section 402(g)(1) of the act. Here, the

comment's suggestion that dietary supplement CGMP requirements could be "modified by manufacturer product specifications" would create uncertainty over whether manufacturers could unilaterally "modify" their product specifications to fit a batch that failed to meet specifications or claim that a violation was "cured" by a manufacturer's new product specification. In any event, given that we decided to omit proposed § 111.2 altogether, the change sought by the comment is moot.

## 2. "Exclusions" (Proposed § 111.6)

As we stated earlier in this section, proposed § 111.6 would exclude from the dietary supplement CGMP requirements persons who engage solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that would be incorporated into a dietary supplement by other persons. However, as we explained in our response to comment 27 of this document, we decided that the exclusion was not necessary, given the changes that we made to final § 111.1(a).

Nevertheless, we received several comments on proposed § 111.6, and we address those comments here.

(Comment 65) One comment would revise the rule to exclude or use different requirements for small businesses. The comment suggested we categorize small businesses by employment levels or dollar sales and adopt a tiered enforcement strategy similar that used in other government programs, such as those under the Occupational Safety and Health Act, the Americans with Disabilities Act, and the Family Leave Act. Another comment would exempt small businesses from the specific requirements for testing if those businesses produce annual batch runs of 25,000 capsules and tablets.

(Response) We decline to exclude small businesses from the final rule or to have different criteria for such businesses. As we stated in our response to comments 1, 3, and 16, there is no reason to assume that Congress meant to apply different or lesser CGMP requirements, or no CGMP requirements at all, to dietary supplements made by small businesses. Dietary supplement CGMP requirements help to ensure the quality of the dietary supplement and, among other things, that a dietary supplement meets its specifications, that it contains the ingredients specified in its master manufacturing record, and that it is not contaminated. Consumers should be able to expect that the dietary supplements they purchase meet CGMP requirements regardless of the manufacturer's size. However, to help businesses comply with dietary supplement CGMPs, we are giving businesses with fewer than 500 employees but 20 or more employees a compliance date of 24 months after the date of publication of this final rule, and we are giving businesses with fewer than 20 employees a compliance date of 36 months after the date of publication of this final rule.

We carefully considered the size of a business when developing these regulations. The most common Small Business Association size standard applicable to manufacturers covered by this final rule is 500 employees. Based on comments and our knowledge of the dietary supplement industry, we know that there are a number of dietary supplement manufacturers who fall significantly below the standard of 500 employees. To accommodate these manufacturers, we have established different compliance dates as noted.

(Comment 66) One comment would exempt "consolidators" (whom it described as individuals who purchase raw agricultural commodities for sale to raw ingredient manufacturers) from the rule. Some comments suggest

expanding the exclusion pertaining to harvesting, storage, and distribution of raw agricultural commodities to include other common and basic raw botanical processing activities, such as drying, chopping, cutting, size reduction, sifting, grinding, and storage. One comment would delete the word “solely” to make the rule more flexible and make it possible to exclude producers, who do not manufacture a distinct product, from the CGMP rule. Another comment expresses concern about potential safety issues that can arise from the early stages of manufacturing, such as the use of improper handling of agricultural commodities and the risk of adulteration; the comment says businesses involved in producing or distributing raw agricultural commodities should be subject to some requirements under the rule. A few comments ask us to draft guidance documents to address activities such as wildcrafting, plant identification, good agricultural practices, and good hygienic practices for wildcrafters (persons who harvest plants grown in the wild), and growers and brokers and specific service providers (millers, extractors). Some comments would exempt individual wildcrafters because wildcrafters deal in relatively small amounts of material at a time and sell their material to larger brokers who combine materials from different pickers together.

(Response) As explained in our responses to comments 29 and 30, persons who only manufacture or supply a component that will be further processed as a dietary supplement by another person are not within the scope of this final rule. Thus, a “consolidator” who simply buys raw agricultural commodities and then sells them to dietary ingredient manufacturers would not be subject to this final rule. Similarly, persons engaged in drying, chopping, cutting, size reduction, sifting, and grinding of raw agricultural commodities which they then sell to others for processing into a dietary

supplement would not be subject to this final rule. We note, however, that such persons are not exempt from other regulatory requirements. We remind readers that a dietary ingredient is a food under section 201(f)(3) of the act. Consequently, a raw agricultural commodity that is a dietary ingredient is still subject to the umbrella food CGMP requirements in part 110, and activities such as drying, chopping, and cutting are what we have long considered to be types of food processing.

As for “wildcrafters,” if they package and label raw agricultural commodities as dietary supplements or sell them to consumers for use as a dietary supplement, we would consider them to be manufacturers of a dietary supplement and subject to the rule. If, however, the wildcrafter simply sells the raw agricultural commodity to another for incorporation into a dietary supplement, it would not be subject to this final rule, but might be subject to the CGMP requirements in part 110. Persons engaged in the harvesting, storage, or distribution of raw agricultural commodities, whether for distribution as a dietary supplement or for distribution as a dietary ingredient to a dietary supplement manufacturer, may want to read our guidance entitled “Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables” available at <http://www.cfsan.fda.gov/~dms/prodguid.html> (Ref. 28). This guidance addresses common areas of food safety concern in the growing, harvesting, sorting, packing, and distribution of fresh produce, and contains principles that would apply to raw agricultural commodities, such as herbs and botanicals.

As for the comment that would delete the word “solely” from proposed § 111.6, we note that such a change is no longer necessary since we are deleting § 111.6. However, we caution that only those persons or entities that

manufacture or supply components that will be further processed as a dietary supplement by others are not subject to the final rule. If you manufacture and sell dietary supplements, in addition to supplying components to others, you would be subject to this final rule under § 111.1(a).

As for potential safety issues arising from the early stages of manufacturing, such as the use of improper handling of agricultural commodities and the risk of adulteration, the final rule, at § 111.75, describes criteria that enable a manufacturer of a dietary supplement to rely on a certificate of analysis. One criterion is that the manufacturer must first qualify the firm providing the component by establishing the reliability of the firm's certificate of analysis through confirmation of the results of the firm's tests or examinations. Firms that improperly handle raw agricultural commodities, such that the commodities that they provide are adulterated, are not likely to be qualified as suppliers of those commodities.

In the future, we will consider the requests to develop guidance for subsets of agricultural and post-harvest activities (such as for hygienic practice for wildcrafters, identifying botanicals) associated with dietary supplement manufacturing, along with other guidance we may find useful as they relate to certain CGMP requirements for dietary supplements.

## **VII. Comments on Personnel (Final Subpart B)**

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

Proposed subpart B contained three provisions regarding personnel. Table 3 of this document lists the sections in final subpart B and identifies the proposed sections that form the basis of the final rule.

TABLE 3.—DERIVATION OF SECTIONS IN FINAL SUBPART B

Final Rule	2003 CGMP Proposal
§ 111.8 What are the requirements under this subpart B for written procedures?	N/A
§ 111.10 What requirements apply for preventing microbial contamination from sick or infected personnel and for hygienic practices?	§ 111.10
§ 111.12 What personnel qualification requirements apply?	§ 111.12
§ 111.13 What supervisor requirements apply?	§ 111.13
§ 111.14 Under this subpart B, what records must you make and keep?	N/A

## *B. Highlights of Changes to the Proposed Requirements for Personnel*

### 1. Revisions

The final provisions in subpart B include revisions that clarify that the final rule applies only to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

The final provisions also include revisions that clarify the applicability of the rule to persons who perform labeling operations for dietary supplements.

### 2. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures to fulfill the requirements of subpart B;
- Provides flexibility regarding the requirement to exclude personnel who might be a source of microbial contamination (e.g., due to illness or open lesions) so that such personnel must be excluded only from operations where such contamination may occur;

- Clarifies that the qualification of personnel and supervisors may be done through education, training, or experience;

- Sets forth a new requirement that you identify qualified personnel to perform quality control operations and requires that such personnel have distinct and separate responsibilities related to performing quality control operations from those responsibilities that the person otherwise has when not performing quality control operations; and

- Sets forth a new requirement to make and keep records that document training of personnel.

### *C. General Comments on Proposed Subpart B*

(Comment 67) Some comments assert one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under section 706(2)(B) of the Administrative Procedure Act (APA) and therefore should be deleted. The comments focus on:

- Proposed § 111.12(a) which would require “qualified employees” and
- Proposed § 111.13(a) which would require “qualified personnel to supervise.”

In general, these comments say the proposal’s failure to define the term “qualified” means that persons who are subject to the rule could not discern the meaning of the term. These comments also say the proposal imposes no limits on enforcement officers as to what would satisfy the requirements and, thus would represent an exercise of unbridled discretion and disparate decisionmaking. These comments argue proposed § 111.12(b), which would require employees to have “the training and experience to perform the person’s duties,” and proposed § 111.13(b), which would require supervisors to be “qualified by training and experience to supervise,” would suffice.

(Response) We are not deleting §§ 111.12(a) and 111.13(a) as requested by these comments. As discussed in section V of this document, we disagree that the terms in question are unconstitutionally vague, need to be defined, or may result in discriminatory enforcement. There has been sufficient common usage of these terms in the food industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms “with a reasonable degree of certainty” to their particular operations (see *Boyce Motor Lines v. United States* 342 U.S. at 340). Further, agencies are permitted to use qualifying terms to enable them to address a wide variety of conditions at companies. For these reasons, we have retained the use of the terms in the final rule. The provisions at issue also give firms the flexibility to determine how to comply with the regulations. We also explain in section V of this document that the final rule does not violate the APA.

*D. What Are the Requirements Under This Subpart for Written Procedures?  
(Final § 111.8)*

We received many comments that recommended written procedures for various provisions. We address the need for written procedures generally in section IV. We also respond to individual comments on specific provisions in the same section. Final § 111.8 requires you to establish and follow written procedures to fulfill the requirements of subpart B. Additionally, to ensure that we can evaluate firms’ compliance with their written procedures, final § 111.14 requires that a person who manufactures, packages, labels, or holds dietary supplements make and keep records of such procedures. Such records would be available to us under subpart P.

*E. What Requirements Apply for Preventing Microbial Contamination From Sick or Infected Personnel and for Hygienic Practices? (Final § 111.10)*

The title of this provision has been changed from proposed § 111.10 to clarify that the requirements are related to the prevention of microbial contamination due to the health condition of personnel and not other sources.

1. Final § 111.10(a)

Final § 111.10(a) requires you to take measures to exclude from any operations any person who might be a source of microbial contamination, due to a health condition, where such contamination may occur, of any material including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement. This provision is similar to proposed § 111.10. We added “due to a health condition” for clarity.

(Comment 68) Several comments suggest that employees who are sick should be allowed to work in areas where they will not come into contact with components, dietary supplements, or contact surfaces, and that the requirements of proposed § 111.10 are too strict. These comments say proposed § 111.10(a) is too broad in stating that such persons be excluded “from working in any operation.” These comments explain that such persons may be suitable for performing other tasks, such as warehouse functions or administrative work. These comments would revise proposed § 111.10(a) so that it is acceptable for such persons to work so long as they will not be a vessel for microbial contamination.

Other comments agree with proposed § 111.10(a), and state that employees who are sick should be excluded from the plant, even from areas where products are not processed. These comments state excluding such personnel

should be mandatory as the microbes from an open sore, wound, or other source of contamination could contaminate the surrounding air, personnel, etc. For example, if the production area is a closed loop air handling system, then contamination could spread to the other areas through the common air handling units/ducts.

(Response) We agree that some tasks may be suitable for a person who might be a source of microbial contamination. Certain warehouse functions or administrative tasks may be appropriate for such a person to do, provided that these functions or tasks do not expose components, dietary supplements, or contact surfaces to microbial contamination from the person, and provided that the person would not infect others who would then expose components, dietary supplements, or contact surfaces to microbial contamination.

A requirement to exclude employees from being present at work would limit potential microbial contamination, which is the basis of the point made by some comments that employees who are sick should be excluded from the plant. However, the comments do not persuade us to deny firms the flexibility to determine whether it would be appropriate for an employee who may be a source of microbial contamination to work in some areas of the physical plant that are sufficiently separated from areas where product contamination could occur. When considering whether an employee may be permitted to work and whether he/she represents a potential source of microbial contamination, one should look beyond the obvious potential sources of contamination, and consider possibilities such as the forms of indirect contamination discussed by the comments. Therefore, we are revising proposed § 111.10(a) to require you to take measures to exclude “from any operations any person who might be a source of microbial contamination, due to a health condition, where such

contamination may occur, of any material including components, dietary supplements, and contact surfaces used in the manufacture, packaging, labeling, or holding of a dietary supplement.”

As one measure to reduce potential microbial contamination, final § 111.10(a)(1) requires you to exclude, from working in any operations that may result in contamination, any person who, by medical examination, the person’s acknowledgement, or supervisory observation, is shown to have, or appears to have an illness, infection, open lesion, or any other abnormal source of microbial contamination, that may result in microbial contamination of components, dietary supplements, or contact surfaces, until the health condition no longer exists. Final § 111.10(a)(1) is similar to proposed § 111.10(a)(1). We have added that the person can acknowledge that he or she may be a source of microbial contamination. We are moving and modifying the prepositional phrase concerning “working in any operation.” We also have added the word “infection” to clarify the sources of potential abnormal contamination.

(Comment 69) Several comments suggest employees who may be the source of microbial contamination should be permitted to work in areas of the plant where they pose no risk of contamination, and therefore should not be excluded unless they pose such a risk.

(Response) We agree with the comments and are revising proposed § 111.10(a)(1) accordingly. Therefore, you may allow persons with certain health conditions to work in areas of a plant where they pose no risk of contamination even though they must be excluded from other areas where they would pose such a risk.

Final § 111.10(a)(2) requires you to instruct your employees to notify their supervisor(s) if they have, or if there is a reasonable possibility that they have, a health condition stated in § 111.10(a)(1) that could contaminate any components, dietary supplements, or any contact surface.

We did not receive comments specific to proposed § 111.10(a)(2).

## 2. Final § 111.10(b)

Final § 111.10(b) requires, if you work in an operation during which adulteration of the component, dietary supplement, or contact surface may occur, you to use hygienic practices to the extent necessary to protect against contamination of components, dietary supplements, or contact surfaces. Final § 111.10(b) lists nine hygienic practices, such as wearing outer garments in a manner that protects against contamination, washing hands thoroughly, and wearing, where appropriate, hair nets, caps, beard covers, or other effective hair restraints.

We did not receive any comments concerning proposed § 111.10(b)(1) (wearing outer garments in a manner that protects against contamination), § 111.10(b)(2) (maintaining adequate personal cleanliness), § 111.10(b)(3) (washing hands thoroughly), § 111.10(b)(4) (removing all unsecured jewelry and other objects that might fall into components, dietary supplements, equipment, or packaging and removing hand jewelry that cannot be adequately sanitized), § 111.10(b)(6) (wearing, where appropriate, hair nets, caps, beard covers, and other effective hair restraints), § 111.10(b)(7) (not storing clothing or other personal belongings where components, dietary supplements, or contact surfaces are exposed or where contact surfaces are washed), and § 111.10(b)(9) (taking any other precautions necessary to protect against contamination).

Proposed § 111.10(b)(5) would require the hygienic practices that you use to include maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition and ensuring that gloves be of an impermeable material.

(Comment 70) One comment asks us to clarify the requirements for the use of gloves in proposed § 111.10(b)(5). The comment says there are situations in which gloves are ineffective or cumbersome. The comment provides as an example, if a person is packaging a bulk material in fiber packs with metal ring lids, bulky gloves can interfere with the finer work such as attaching security tabs, and thin, flexible gloves can be easily damaged by the sharp edges of the metal rings on the lid.

(Response) Final § 111.10(b)(5) requires you to maintain gloves in an intact, clean, and sanitary condition; it does not require you to use gloves in any specific situation. Although there is no requirement for wearing gloves while performing specific operations, you must wear gloves when they are necessary to protect against contamination of any components, dietary supplements, or contact surfaces.

(Comment 71) Proposed § 111.10(b)(8) would require that the hygienic practices that you use, to the extent necessary to protect against contamination, include not eating food, chewing gum, drinking beverages, or using tobacco products in areas where components, dietary ingredients, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed.

One comment would substitute the word “processed” for the word “exposed” in proposed § 111.10(b)(8). The comment says, although areas where components, dietary supplements, and contact surfaces are exposed pose the greatest risk, adulteration is also possible where these items are held

(i.e., stored in containers and, thus, not exposed). Furthermore, the comment explains the use of the word “processed,” rather than “exposed,” would cover all areas intended to be covered by CGMPs and would alleviate the need to specify that the requirement applies to areas where contact surfaces are washed.

(Response) We decline to revise the rule as suggested by the comment. We believe the word “exposed” covers all areas intended to be covered by the requirement, including areas where contact surfaces are washed. We consider an area where contact surfaces are washed to “expose” the contact surface. To avoid any confusion, we are modifying § 111.10(b)(8) to say “\* \* \* any contact surfaces are exposed, or where contact surfaces are washed.” As written, the requirement to not eat, chew gum, drink, or use tobacco products in areas where components, dietary supplements, and contact surfaces are exposed gives firms appropriate flexibility to determine areas where employees may or may not eat, chew gum, drink, or use tobacco products.

*F. What Personnel Qualification Requirements Apply? (Final § 111.12)*

Final § 111.12(a) requires you to have qualified employees who manufacture, package, label, or hold dietary supplements. Final § 111.12(a) is similar to proposed § 111.12(a), except that the final rule includes an editorial change to clarify that the requirement is to have the qualified employees do the work rather than merely to have qualified employees.

(Comment 72) The 2003 CGMP Proposal invited comment on whether there is a minimum number of employees needed to manufacture dietary supplements (68 FR 12157 at 12183). Several comments state the final rule should not include such a minimum number because firms should be able to decide for themselves how many qualified personnel they need.

(Response) The final rule does not stipulate a minimum number of employees. However, there should be enough employees to manufacture, package, label, and hold dietary supplements to ensure compliance with the final rule. In general, CGMP suggests the need for a minimum of two persons: One to perform the work, and a second to check the work performed to ensure that a manufacturing deviation or an unanticipated occurrence is not overlooked.

(Comment 73) Some comments about the proposed definition of “quality control unit” say the quality control function need not be performed by a distinct or separate unit. These comments say the quality control function is best performed by a person or persons qualified by training, education, or experience in the different processing areas.

(Response) As discussed, we have revised the proposed definition and substituted the term “personnel” for “unit.” (For the definition of quality control personnel, see section VI of this document.) We agree the quality control functions do not need to be performed by a distinct or separate unit or person and that a person who is qualified by training, education, or experience can serve a quality control function. Therefore, we are adding a new § 111.12(b) to clarify that you must identify who is responsible for quality control operations. Under final § 111.12(b) each person identified must be qualified to perform such operations, and must have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations. The quality control personnel can have dual functions within the facility but should separately perform the different responsibilities.

Final § 111.12(c) requires that each person engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, have the education, training, or experience to perform the person's assigned functions. Final § 111.12(c) includes a revision associated with final § 111.12(b) by including persons who perform quality control operations as persons who also need to have the education, training, or experience for the assigned functions.

(Comment 74) Several comments state we should revise the rule to allow for any combination of "training or experience." These comments explain it is not always possible for an employee to have both "training and experience." These comments would revise proposed § 111.12(b) to read, "each person engaged in the manufacture of a dietary product should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. Training should be in the particular operations(s) that the employee performs as they relate to the employee's functions." Another comment asks for guidance as to what type of education, training, or experience is required for an employee to be considered qualified.

(Response) We agree with the point made by the comments. We acknowledge that some positions will require an appropriate educational background in addition to any on-the-job training. In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12183) we noted "training" may be considered a form of "education" and elected to require that employees be qualified by "training and experience" rather than "education, training, and experience." The 2003 CGMP Proposal used the conjunction "and" because we considered "experience" to be different from training, in that "experience" is knowledge

that a person gains over time, e.g., as he or she becomes increasingly familiar with a particular action or piece of equipment.

These comments persuade us that the rule would be clearer if we added “education” to the list of attributes that are used to qualify an employee. We also agree there are some employees who could be qualified based solely on their education or experience and other employees who would become qualified through, for example, on-the-job training before they are left on their own to perform their assigned duties. Rather than revise the rule to list all three attributes and then explain that an employee can be qualified by any combination of the attributes, we have changed the conjunction from “and” to “or.” Additionally, on our own initiative, we have replaced “person’s duties” with “person’s assigned functions.” This change reinforces the principle that the employee’s training relates to the functions that he or she is assigned to perform.

We will consider whether it would be useful to provide guidance on what type of education, training, or experience would be sufficient for an employee to be properly qualified. We believe that such education, training, or experience may vary by job function and that it would be difficult to provide generic guidance that would be sufficient for all specific job tasks. We decline to suggest that training should be limited, as the comments suggest, to the particular operation(s) that the employee performs as they relate to the person’s functions. These CGMP requirements apply to many types of manufacturing operations of various size and complexity, so the training may vary depending on the circumstances and may include more than the employee’s assigned functions.

(Comment 75) One comment states we should provide training materials such as texts, videos, Internet training, or seminars, to help companies properly train their employees.

(Response) We have no plans at this time to provide companies with training materials for their employees. We expect that most companies already have trained or will train their employees and that where additional training is needed to comply with these regulations, companies will develop the training materials that are appropriate for the functions their employees perform. We may consider providing guidance in the future if circumstances warrant such guidance.

*G. What Supervisor Requirements Apply? (Final § 111.13)*

Final § 111.13(a) requires you to assign qualified personnel to supervise the manufacturing, packaging, labeling, or holding of dietary supplements. Final § 111.13(a) derives from proposed § 111.13(a).

We did not receive comments specific to proposed § 111.13(a).

Final § 111.13(b) requires each supervisor you use to be qualified by education, training, or experience to supervise. Final 111.13(b) derives from proposed § 111.13(b) which would require you and your supervisors to be qualified by training and experience to supervise.

(Comment 76) Several comments ask us to revise the rule so that supervisors may be qualified by any combination of training or experience. These comments would revise proposed § 111.13(b) to read, “supervisors must be qualified by education, training, and experience (or any combination thereof) to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements in compliance with this rule.” One comment, however, would make an exception for quality control and

sanitation supervisors, stating we should require these supervisors to have both training and experience.

(Response) Consistent with the change we made to proposed § 111.12(c), we are revising proposed § 111.13(b) to require the supervisors you use to be qualified by “education, training, or experience.” We acknowledge that some supervisory personnel may need a different range of education, training, or experience than others, and expect firms to determine the appropriate balance of education, training, and experience.

(Comment 77) Several comments say our use of the phrase “you and the supervisors you use” in proposed § 111.13(b) was unclear. According to these comments, the term “you” as defined in the proposal, is quite expansive and could be read so broadly as to require the Chief Executive Officer (CEO) of a company be “qualified” to supervise.

(Response) We agree that the phrase “you and the supervisors you use” could be clearer. Therefore, we are revising proposed § 111.13(b) to say that “each supervisor whom you use” must be qualified to supervise. Section 111.13(b) applies to any person who supervises the manufacturing, packaging, labeling, or holding of dietary supplements, even if that person also is an executive such as the CEO. Thus, final § 111.13(b) states, “Each supervisor whom you use must be qualified by education, training, or experience to supervise.”

(Comment 78) Several comments say the term “to supervise” is ambiguous and would revise the rule to clarify what a supervisor must be qualified to supervise: The manufacture, packaging, or holding of dietary ingredients and dietary supplements. Another comment would revise proposed § 111.13(b) to clarify what type of training and experience are required so that firms would

have more guidance as to what is expected to confirm that personnel are qualified.

(Response) We decline to revise the rule as suggested by the comments. We disagree that the term “to supervise,” which is commonly used in the industry, is ambiguous. These CGMP requirements apply to many types of manufacturing operations of various size and complexity, and the training must be suited to the circumstances.

*H. Under This Subpart, What Records Must You Make and Keep? (Final § 111.14)*

As discussed in this section, the final rule contains a new § 111.8 requiring you to establish and follow written procedures to fulfill the requirements of subpart B. Those written procedures are records. Therefore, we are adding a new § 111.14(a) requiring you to make and keep records in accordance with subpart P. Final § 111.14(b)(1) requires you to make and keep a record of the written procedures for fulfilling the requirements of subpart B.

The preamble to the 2003 CGMP Proposal invited comment on whether we should require documentation and records regarding each employee’s training (68 FR 12157 at 12183). After considering comments and for the reasons discussed in the following paragraphs, § 111.14(b)(2) requires you to make and keep documentation of training, including the date of training, the type of training, and the person(s) trained.

We also invited comment on whether the final rule should contain requirements for documentation about consultants that you use (68 FR 12157 at 12183). We specifically suggested any such requirement include the consultant’s name, address, qualifications, and a description of services provided. After considering the comments and for the reasons discussed in

the following paragraphs, the final rule does not include any requirements to make and keep records regarding consultants.

(Comment 79) Several comments state employee training records are critical and should be required under the final rule. The comments explain that these records should show the content of the training, the date of the training, and the signature of the employee trained. These comments assert that a formal (written) GMP training program is necessary to track which employees have been trained in the CGMP requirements. These comments add, without a written and documented training program, it is likely that some employees may not receive sufficient training, or in some cases, any CGMP training at all. These comments say successful quality control programs are inextricably connected to appropriate training programs, and written documentation of employee training is an important safeguard to ensuring safe and accurately labeled dietary supplements. These comments also state it is already an industry standard to document training.

Other comments question our ability to evaluate whether a firm's employees have been adequately trained without written documentation of the training.

(Response) As discussed more fully in the discussion of subpart E in section X of this document, the final rule focuses on ensuring the quality of the dietary supplement at every stage of the production and process control system. Such a system begins with the proper training. We agree that documentation of employee training is necessary to track which employees have been trained in which operations. Therefore, final § 111.14(b)(2) requires you to keep documentation of training, including the date of the training, the type of training, and the person(s) trained.

(Comment 80) One comment says we should not require manufacturers to document and keep records regarding each employee's training. The comment says the rule should focus on end results and not on process.

(Response) We disagree with the comment. As we have explained in this section, each person engaged in an activity covered by these CGMP regulations must have the education, training, or experience to perform the person's assigned functions. Some employees will be considered qualified based in part on training taken as company employees. To show that such training is appropriate to the employee's functions and has in fact occurred, the training must be properly documented. This documentation is an important aspect of ensuring adequate training and, therefore, helping to ensure the result of having qualified employees who perform their functions properly.

(Comment 81) Several comments state the documentation of the training program should include the title of the person doing the training, an evaluation of the employee's understanding of the training, and recommendations for the frequency of refresher training. One comment describes a specific method for training and for tracking training. The comments state an evaluation of the employee's understanding of the training would ensure that employees who receive training understand what they have been taught.

(Response) We decline to require specific additional documentation of employee training. We believe a firm should have some flexibility in how it wants to document training.

(Comment 82) Several comments respond to our question as to whether the final rule should require documentation about consultants, including each consultant's name, address, qualifications, and a description of services provided. Several comments say that documenting this information is useful

and could be done on a voluntary basis, but that such information is not necessary to ensure safe and accurately labeled supplements and, thus, should not be required. One comment notes that recommendations from consultants may or may not be used, and that a company should not have to explain at a later date why such decisions were made. Another comment asserts that we and the company may have different opinions on whether a consultant is qualified and that the consultant's qualification is not our concern if a product is not adulterated. One comment says documenting the name and services of the GMP consultants should be required to facilitate contact in case of need.

(Response) The proposal noted documentation of the name, address, qualifications, and services rendered for each consultant may help you know whom to contact and if questions arise concerning the advice that the consultant has given. Thus, our intent in suggesting such documentation was to help you rather than to make the information available for us to determine whether we agreed with you that a particular individual was qualified to be a consultant. However, the comments persuade us that such information is not necessary to help ensure dietary supplement quality. Therefore, the final rule does not require documentation regarding consultants.

## **VIII. Comments on Physical Plant and Grounds (Final Subpart C)**

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

Proposed subpart C contained two provisions regarding physical plants. Table 4 of this document lists the sections in final subpart C and identifies the corresponding proposed sections that form the basis of the final rule.

TABLE 4.—DERIVATION OF SECTIONS IN  
FINAL SUBPART C

Final Rule	2003 CGMP Proposal
§ 111.15 What sanitation requirements apply to your physical plant and grounds?	§ 111.15
§ 111.16 What are the requirements under this subpart C for written procedures?	N/A
§ 111.20 What design and construction requirements apply to your physical plant?	§ 111.20
§ 111.23 Under this subpart C, what records must you make and keep?	§ 111.15(d)(3) and (e)(2)

## *B. Highlights of Changes to the Proposed Requirements for Physical Plant and Grounds*

### 1. Revisions

The final rule:

- Reflects that the rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.
- Requires you to have documentation or otherwise be able to show that water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, meets applicable Federal, State, and local requirements and does not contaminate the dietary supplement.

### 2. Changes After Considering Comments

The final rule:

- Includes requirements similar to the food CGMP requirements in § 110.20(a) for keeping the grounds bordering your physical plant in a condition that protects against contamination.

- Clarifies that sanitation supervisors can be qualified by education, training, or experience.
- Modifies the minimum requirements for water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface. Such water must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement.
- Simplifies the sanitation requirements for toxic materials, bathroom facilities, and hand-washing facilities.
- Simplifies and clarifies the design requirements for floors, walls, and ceilings; fans and other air-blowing equipment; equipment that controls temperature and humidity; and the use of safety-type glass or glass-like materials.
- Requires written procedures for cleaning the physical plant and for pest control.
- Requires that you make and keep records of the written procedures.

### *C. General Comments on Proposed Subpart C*

(Comment 83) Several comments say we should have different sanitation requirements for dietary ingredient manufacturers than for dietary supplement manufacturers. These comments state that the manufacture of synthetic or highly processed dietary ingredients includes extensive purification steps, especially toward the end of the manufacturing process, and that these steps remove contaminants that may have been introduced at earlier stages in the manufacturing process. These comments consider some stages of the dietary ingredient manufacturing process to not be subject to the same strict controls as those used for manufacturing finished dietary supplements.

(Response) As discussed in section VI of this document (subpart A), the final rule applies to persons who manufacture, package, label, or hold dietary supplements and who are not subject to an exclusion in § 111.1, and does not apply to establishments that only manufacture dietary ingredients. We addressed this comment in the response to comment 29.

(Comment 84) Some comments assert that one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and are arbitrary and capricious under section 706(2)(B) of the APA. The comments would delete the following proposed requirements:

- § 111.15(e), which would require plumbing to be “of an adequate size and design and be adequately installed and maintained;”
- § 111.15(g), which would require bathrooms to be “adequate” and “readily accessible; ”
- § 111.15(h), which would require hand-washing facilities “to be adequate, convenient, and furnish running water at a suitable temperature;”
- § 111.15(h)(i), which would require hand-washing and, where appropriate, hand-sanitizing facilities “at each location in your physical plant” where good hygienic practices require employees to wash or to sanitize or both wash and sanitize their hands;
- § 111.20(a), which would require your physical plant to “be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;” and
- § 111.20(d)(6), which would require aisles or working spaces between equipment and walls to be adequately unobstructed and of adequate width.

In general, these comments assert the 2003 CGMP Proposal did not define terms or phrases (such as “adequately” or “at each location”) in a way that persons who are subject to the rule can discern the meaning of the term or

phrase. These comments argue that the proposed rule imposes no limitations on enforcement officers on the exercise of their discretion and, thus, invites exercise of unbridled discretion and disparate decisionmaking.

(Response) As discussed in section V of this document, we disagree that the terms that the comments objected to in the 2003 CGMP Proposal are unconstitutionally vague, need to be defined, or may result in discriminatory enforcement. We are retaining the terms in the final rule.

*D. What Sanitation Requirements Apply to Your Physical Plant and Grounds?*

*(Final § 111.15)*

1. Final § 111.15(a)

The preamble to the 2003 CGMP Proposal (68 FR 12157 at 12184) stated that we were not proposing requirements similar to the food CGMP requirements found in § 110.20(a) for keeping the grounds bordering your physical plant in a condition that protects against contamination of components or dietary supplements in order to limit the burden to manufacturers. However, we invited comment on whether we should include such requirements in a final rule. After considering the comments, we have drafted final § 111.15(a) to require you to keep the grounds of your physical plant in a condition that protects against the contamination of components, dietary supplements, or contact surfaces. The methods for adequate ground maintenance include:

- Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the physical plant so that it does not attract pests, harbor pests, or provide pests a place for breeding;

- Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed;

- Adequately draining areas that may contribute to the contamination of components, dietary supplements, or contact surfaces by seepage, filth or any other extraneous materials, or by providing a breeding place for pests;

- Adequately operating systems for waste treatment and disposal so that they do not constitute a source of contamination in areas where components, dietary supplements, or contact surfaces are exposed; and

- If your plant grounds are bordered by grounds not under your control, and if those other grounds are not maintained in the manner described in this section, you must exercise care in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth or any other extraneous material that may be a source of contamination.

(Comment 85) Several comments say the final rule should require the maintenance of external areas similar to the food CGMP requirement at § 110.20(a) for keeping the grounds outside the facility adequately maintained. These comments state that such a requirement is basic, is equally important to facilities that manufacture conventional foods and to facilities that manufacture dietary supplements, and that there is no reason why this requirement should differ from food CGMPs. One comment asserts such a requirement is basic to the industry and it should not be dismissed as a burden to the industry. Some comments also assert that a provision similar to § 110.20(a) would help train staff and would explain to plant maintenance personnel what is required and why.

One comment says there should be some minimum requirement for sanitation and cleanliness in the area surrounding the plant and that requirements for drainage and trash removal should be adequate.

(Response) We agree that a requirement to maintain grounds is equally important for facilities that manufacture conventional foods and for facilities that manufacture dietary supplements. Although some requirements in § 110.20(a) are not strictly limited to drainage and trash disposal, the comment suggesting the requirements to maintain grounds be limited to drainage and trash disposal did not explain why, for example, it would not be as important for a facility that manufactures dietary supplements to maintain roads, yards, and parking lots so that they do not become a source of contamination as it already is for facilities that manufacture conventional foods. Therefore, the final rule is adding § 111.15(a), which is similar to § 110.20(a) with editorial revisions consistent with the rest of this final rule.

## 2. Final § 111.15(b)(1)

Final § 111.15(b)(1) (proposed § 111.15(a)) requires you to maintain your physical plant in a clean and sanitary condition. Final § 111.15(b)(2) requires you to maintain your physical plant in repair sufficient to prevent components, dietary supplements, or contact surfaces from becoming contaminated.

We did not receive comments specific to proposed § 111.15(a).

## 3. Final § 111.15(c)

Final § 111.15(c) (proposed § 111.15(b)) sets forth requirements for cleaning compounds, sanitizing agents, pesticides, and other toxic materials.

Final § 111.15(c) includes changes that we are making for clarity and consistency. We added other “toxic” materials because some paragraphs within final § 111.15(c) simply refer to the cleaning compounds, sanitizing

agents, and pesticides as “toxic materials,” and because proposed § 111.15(b)(2) addressed the use and storage of toxic materials that are not within the general category of cleaning compounds, sanitizing agents, or pesticides.

Final § 111.15(c)(1) requires you to use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and that are safe and adequate under the conditions of use. Final § 111.15(c)(1) is similar to proposed § 111.15(b)(1), except that we inserted “that are” before “safe and adequate.” We consider this to be a nonsubstantive, editorial change. Proposed § 111.15(b)(1) was, itself, patterned after § 110.35(b)(1), which: (1) Requires cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures to be free from undesirable microorganisms and safe and adequate under the conditions of use and (2) provides that compliance may be verified by any effective means including purchase of these substances under a supplier’s guarantee or certification or examination of these substances for contamination.

(Comment 86) Several comments ask us to clarify our expectations with respect to substantiating that a cleaning compound or sanitizing agent is free from microorganisms of public health significance and is safe and adequate under conditions of use. Some comments suggest proposed § 111.15(b)(1) provide for the use of certifications or guarantees from a supplier because our investigators otherwise may not recognize such documents as evidence of compliance. Several comments say it is not necessary for a manufacturer to test these types of products, and that a continuing product guarantee, combined with a statement of intended use from the manufacturer of the cleaning compound or sanitizing agent, should satisfy the requirements.

(Response) When assessing compliance with final § 111.15(c)(1), we would not treat a firm that manufactures, packages, labels, or holds a dietary supplement differently than we would treat a facility that manufactures, packages, labels, or holds conventional foods. Therefore, we intend to accept, as the comments request, a supplier's guarantee or certification that a cleaning compound or sanitizing agent is free from microorganisms of public health significance and is safe and adequate under the conditions of use for the purpose of determining compliance with final § 111.15(c)(1).

Final § 111.15(c)(2) requires you to not use or hold toxic materials in a physical plant in which components, dietary supplements, or contact surfaces are manufactured or exposed, unless those materials are necessary: (1) To maintain clean and sanitary conditions, (2) for use in laboratory testing procedures, (3) for maintaining or operating the physical plant or equipment, or (4) for use in the plant's operations.

We did not receive comments specific to proposed § 111.15(b)(2). We have made a nonsubstantive edit to § 111.15(c)(2) by moving "contact surfaces" to be the last item on the list.

Final § 111.15(c)(3) requires you to identify and hold cleaning compounds, sanitizing agents, pesticides, pesticide chemicals, and other toxic materials in a manner that protects against contamination of components, dietary supplements, or contact surfaces. Final § 111.15(c)(3) is similar to proposed § 111.15(b)(3).

We did not receive comments specific to proposed § 111.15(b)(3), but replaced "toxic cleaning compounds" with "cleaning compounds," and added "other toxic materials."

#### 4. Final § 111.15(d)

Final § 111.15(d) (proposed § 111.15(c)) sets forth requirements for pest control. Section § 111.15(d) is almost identical to proposed § 111.15(c).

Final § 111.15(d)(1) requires you to not allow animals or pests in any area of your physical plant. Final § 111.15(d)(1) allows guard or guide dogs in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary supplements, or contact surfaces. Final § 111.15(d)(2) requires that you take effective measures to exclude pests from your physical plant and to protect against the contamination of components, dietary supplements, and contact surfaces on the premises by pests. Final § 111.15(d)(3) requires that you not use insecticides, fumigants, fungicides, or rodenticides unless you take precautions to protect against the contamination of your components, dietary supplements, or contact surfaces.

(Comment 87) Several comments claim proposed § 111.15(c) would require that sealed equipment outside of the plant (e.g. storage tanks, vessels, piping) be enclosed to prevent pests from roaming around these areas. The comments say there is no need to shelter outdoor equipment if it is properly sealed. These comments state that dietary supplements are sometimes manufactured in extensive, highly automated facilities in which large tanks and vessels are interconnected via piping, and that in these cases “the physical plant” and “the equipment in the plant” converge so that some or much of the equipment is effectively located outdoors. Thus, the comments ask us to revise proposed § 111.15(c) to clarify that it applies only to interior areas of the physical plant.

(Response) Equipment such as that described by the comments, if properly sealed, should protect components, dietary supplements, and contact surfaces from contamination with pests. Final § 111.15(d) does not require that sealed

equipment outside of the plant, such as storage tanks, vessels, or piping, be enclosed, e.g., inside a building. Final § 111.15(d)(2) requires that you take effective measures to exclude pests from your physical plant and to protect against the contamination of components, dietary supplements, or contact surfaces on the premises by pests. Moreover, final § 111.15(a) includes several requirements designed to limit or exclude pests around all parts of the exterior of your physical plant. Therefore, although you do not have to enclose your outside equipment, you must take measures to exclude pests from areas outside of the plant.

#### 5. Final § 111.15(e)

Final § 111.15(e) (proposed § 111.15(d)) sets forth requirements for the water supply of your physical plant.

Final § 111.15(e)(1) requires that you must provide water that is safe and sanitary at suitable temperatures and under pressure as needed for all uses where water does not become a component of the dietary supplement.

We did not receive comments specific to proposed § 111.15(d)(1). We have modified the phrase “safe and of adequate sanitary quality” to read “safe and sanitary.” To avoid confusion with the definition of “quality” we have adopted solely for purposes of this final rule, we deleted the references to “quality” as it applies to water standards. We consider this change to be nonsubstantive and still require water that is not a component of a dietary supplement to meet a safe and sanitary standard.

Final § 111.15(e)(2) requires that water used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements

and not contaminate the dietary supplement. Final § 111.15(e)(2) derives from proposed § 111.15(d)(2) which would require that water that contacts components, dietary supplements, or any contact surfaces must, at a minimum, comply with the applicable National Primary Drinking Water (NPDW) regulations and any State and local government requirements. Final § 111.15(e)(2) includes changes we are making after considering comments discussed in the following paragraphs.

(Comment 88) Several comments state the water quality that is required for conventional foods is sufficient for dietary supplements. The comments argue that no additional water standards are listed in the CGMPs for low-acid canned foods in part 113 or in the CGMPs for acidified foods in part 114. These comments argue that, if “safe and of adequate sanitary quality” is sufficient to ensure the quality of the water used in most food products, then it is also adequate to ensure the quality of the water used in dietary supplements.

Other comments would revise the final rule to allow different standards and requirements for water that contacts or is used in dietary supplements compared to water that contacts components, including dietary ingredients. These comments state current food CGMP regulations require only that water supplies that contact food (defined to include ingredients and raw materials) be “safe and of adequate sanitary quality.” These comments say that this would be consistent with the act’s basis for CGMP requirements for foods, i.e., that food is not prepared “under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health” (section 402(a)(4) of the act). Several comments state the final rule should adopt a similar rationale for components, including dietary ingredients. These comments explain that components, including dietary

ingredients, are not in a form in which they will be consumed and are subject to further processing prior to consumption.

Several comments say that requiring water used for cleaning contact surfaces to meet Environmental Protection Agency regulations is an unnecessary burden for companies that do not have access to municipal water. According to these comments, potable water should be sufficient.

(Response) In the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12185), we stated that water should, at a minimum, be potable and that water that is "safe and of adequate sanitary quality" should be potable. We also said water that contacts components, dietary supplements, or contact surfaces should, at a minimum, meet the Environmental Protection Agency's NPDW regulations and State, and local requirements. We proposed to require that water used in operations where water contacts components, dietary supplements, or any contact surfaces meet the NPDW regulations because of the potential for contamination if water were used that did not adhere to the microbial standards, for example, in the NPDW regulations. Finally, we stated these requirements were minimum requirements and that water that is more pure than that required under the NPDW regulations may be desired.

The comments stated some manufacturers may not have access to municipal water, and therefore, that meeting the NPDW regulations for cleaning contact surfaces would be too burdensome. These comments asserted that potable water would be sufficient. The comments do not provide a definition of "potable water." We have defined "potable water," in the regulations on interstate conveyance sanitation in 21 CFR part 1250 to be, in part, water that meets the standards prescribed in the Environmental Protection Agency's NPDW regulations in 40 CFR part 141.

We would consider it to be a rare situation where a dietary supplement manufacturer uses well water and has no access to municipal water. Nonetheless, to the extent that a manufacturer uses water that is not subject to Federal oversight, the manufacturer would have to comply with any State or local regulations that apply to food manufacturing facilities using such water in food processing.

Manufacturers that use water from a municipal source, which is subject to the Environmental Protection Agency NPDW regulations, should not be subject to a lesser standard in this final rule than what is already required of them by the Environmental Protection Agency. Thus, to accommodate manufacturers subject to the Environmental Protection Agency's NPDW regulations for the water that they use in the manufacture of dietary supplements, as well as those dietary supplement manufacturers who are not subject to the Environmental Protection Agency's NPDW regulations, we are modifying the rule to state water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. We decline to use "safe and of adequate safety" that some comments state is sufficient because it is for conventional foods. We believe that requiring that water comply with Federal, State and local requirements and not contaminate dietary supplements provides a clear standard as to what is required.

(Comment 89) Some comments assert that water that is used to manufacture components or dietary ingredients where such components or dietary ingredients are subject to further processing prior to consumption,

should be subject to the “safe and of adequate sanitary quality” standard in § 110.37.

(Response) We acknowledge that such components and dietary ingredients are subject to the requirement in § 110.37. If the manufacturers do not fall within the scope of final § 111.1, such manufacturers would be subject to the CGMP requirements in part 110.

To the extent that such comments request the “safe and of adequate sanitary quality” language apply to water used in the manufacture of a dietary supplement, we decline to make that change. Water that is safe and sanitary would not necessarily comply with, for example, the NPDW regulations. A requirement stating “safe and of adequate sanitary quality” or, as stated in the final rule, the requirement of “safe and sanitary” could be seen as a lesser standard than water that complies with “applicable Federal, State, and local requirements.” We want to make clear that you must comply with applicable Federal, State, and local requirements related to the water that you use for food processing that would otherwise be required of you, and not to some lesser standard that you may consider is “safe and sanitary” when water is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts a component, dietary supplement, or any contact surface. Foreign manufacturers would need to comply with the water standard required in this final rule and achieve the same level of performance as is required of domestic manufacturers. The water used in domestic or foreign manufacturing must not contaminate the dietary supplement. To clarify that the water used, whether by a domestic or foreign manufacturer, must not be a source of contamination, we are adding the words “and not contaminate the dietary supplement” in final § 111.15(e)(2). We also

want to make it clear that water includes what is in the water, e.g., any of its contaminants in addition to H<sub>2</sub>O. For example, when we speak of drinking water, we do not just mean the H<sub>2</sub>O, we mean the iron, lead, sulfur, and any other contaminants contained in the water.

(Comment 90) Several comments suggest water should meet some or all standards of the USP monograph for sterile, purified water and say that the standard in the USP monograph is a higher, and presumably safer, standard than the NPDW standard. The comments state the USP's water deionization and purification systems requirements are already common in the industry.

(Response) We do not discourage firms from using water in dietary supplement manufacturing that meets USP standards, including deionized or purified water, but we do not require, as a CGMP, the use of USP standards. This final rule sets forth minimum requirements for persons who manufacture, package, label, or hold a dietary supplement. Thus, firms may use water that exceeds our minimum requirements.

(Comment 91) The preamble to the 2003 CGMP Proposal recognized that foreign firms might not be subject to Environmental Protection Agency water requirements or adhere to such requirements, but also stated that water quality is an important part of CGMP (68 FR 12157 at 12185). Thus, in the preamble to the 2003 CGMP Proposal, we invited comment on how we might ensure that foreign firms meet the same water quality requirements as domestic firms. Several comments respond to our request for comments specific to the applicability of the water standards to foreign firms. Several comments recommend we not distinguish between domestic and foreign firms with regard to water quality. The comments claim all firms must compete on a "level playing field." These comments state water quality standards vary from

country to country, and many countries do not have requirements that are comparable to those in the United States. The comments say foreign manufacturers should not be permitted to import products into the United States that do not meet the same safety standards as domestic goods.

Other comments ask us to consider the water quality requirement to be met if the water complies with the NPDW standard or any equivalent water quality standard that is ensured by a foreign public agency.

(Response) We agree that foreign firms should be required to meet the water safety and sanitary requirements required of domestic firms and achieve the same level of performance of domestic firms. As discussed in this section, foreign firms are required to meet all requirements and would need to comply with their own national or local water safety requirements and not contaminate the dietary supplement.

(Comment 92) One comment would combine proposed § 111.15(d)(1) and (d)(2) into a single paragraph. The comment says the two proposed paragraphs are redundant. Proposed § 111.15(d)(1) would require that you provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for: (1) Manufacturing dietary ingredients or dietary supplements; (2) making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces; (3) cleaning any surface; and (4) employee bathrooms and hand-washing facilities. Proposed § 111.15(d)(2) would require that water that contacts components, dietary ingredients, dietary supplements, or any contact surface must at a minimum comply with the NPDW regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any State and local government requirements.

(Response) We disagree that proposed § 111.15(d)(1) and (d)(2) were redundant. For example, as described in the proposed sections, nonpotable water that would have been “safe and of adequate sanitary quality” for use in flushing toilets may not have been “safe and of adequate sanitary quality” for use in the manufacture of a liquid dietary supplement.

Final § 111.15(e)(1) requires that you provide water that is safe and sanitary, at suitable temperatures, and under pressure as needed, for all uses where water does not become a component of the dietary supplement. Final § 111.15(e)(2) requires that water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the dietary supplement. As an example of how the requirements would apply, water that contains lead at a level that is 20 times higher than the maximum accepted level in the Environmental Protection Agency’s NPDW standards for lead may not be safe for use in the manufacture of dietary supplement that is consumed in four 2-ounce portions per day, but may be safe for use in cleaning the floors of the physical plant. Therefore, to emphasize that water that is “safe and sanitary” may be different depending on its use, the final rule continues to separate § 111.15(e)(1) and (e)(2) (formerly proposed § 111.15(d)(1) and (d)(2)).

Additionally, to emphasize the importance of the water that is used in the manufacture of a dietary supplement, where the water is used in a manner such that the water may become a component of the dietary supplement, final § 111.23(c) (proposed § 111.15(d)(3)) requires you to have documentation and keep records that such water meets the requirements of final § 111.15(e)(2).

In contrast, there is no corresponding requirement for documentation in final § 111.23 that other water, such as water that is used to clean floors or used in employee bathrooms, meets requirements of final § 111.15(e)(1).

(Comment 93) Several comments state, if we retain a water standard requirement based on the Environmental Protection Agency NPDW standard, then it is important to include provisions recognizing the acceptability of municipal water sources and the frequency of testing required for other water sources. Some comments recommend water should meet the USP standard for purified water and point out that the USP standard provides an assurance of the water's consistency and provides a system that can be monitored.

Several comments suggest we include timetables for water testing or describe water testing frequency requirements. These comments state we should apply something analogous to the proposed requirements for infant formula which would require manufacturers to conduct the tests with sufficient frequency to ensure that the water meets the Environmental Protection Agency's NPDW standard, but not less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants. Other comments refer to the amendments to the bottled water regulations at § 165.110 which require a minimum yearly monitoring of source water and finished bottled water products for chemical contaminants for which allowable levels have been established in the bottled water quality standard.

(Response) Final § 111.23(c) requires you to have documentation that water, when used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts a component, dietary supplement, or contact surface, meets the requirements of final § 111.15(e)(2).

You must meet the requirement for final § 111.15(e)(2) at the point of use, rather than at the point of delivery, i.e., at the point the water may become a component of the dietary supplement, such as when the water contacts components, dietary supplements, or any contact surface (such as when the water comes out of the faucet or comes out of a spigot from a holding tank where you store water). Thus, you must ensure that the water used in a manner such that the water may become a component of the dietary supplement, not the water source before it enters your facility, meets the NPDW regulations, or if not subject to the NPDW regulations, that it meets any other applicable Federal, State, and local requirements and does not contaminate the dietary supplement.

For example, if the water that enters your facility is subject to the Environmental Protection Agency NPDW regulations, then the water must comply with such requirements at the point of use, i.e., when it contacts the components, dietary supplement, or any contact surface (such as when the water comes out of the faucet or out of a spigot from a holding tank where you store water). You could rely on a certificate of analysis under final § 111.75(a)(2)(ii) from the supplier of the water (e.g., the municipality) to ensure that the water entering your facility complies the applicable Federal, State, and local requirements. However, you must ensure that nothing happens to the water that may contaminate the water once it enters your facility and before the water may become a component of the dietary supplement at the point of use. Certain contaminants or microorganisms may be introduced into the water from the facility. Thus, you may need to establish specifications and procedures to prevent contamination from pipes through which the water travels in the facility or from vessels in which the water is held in the facility

prior to use. You may need to test for certain contaminants, e.g., lead or microorganisms, at point of use to ensure there is no contamination of the water within your facility. Such tests may not need to include all of the chemical, microbiological, or contaminant testing already certified by the supplier to determine whether the water entering your facility complies with Federal, State and local requirements. Rather, you would need to evaluate what, if any, introductions of contaminants are likely to occur within your facility and determine whether additional tests are needed to verify that the water, at point of use, will comply with Federal, State, and local requirements and not contaminate the dietary supplement. Alternatively, you may decide not to rely on a certificate of analysis and instead conduct your own testing at point of use to determine if the water complies with applicable Federal, State, and local requirements. We decline to set out testing requirements or frequency of testing in this final rule in lieu of giving manufacturers the flexibility to decide on the appropriate testing and frequency of such testing to ensure that the water meets the requirements in final § 111.15(e)(2). We may consider issuing guidance, as needed, on our recommendation for testing based on water sources and the purposes for which the water is used. If you rely on a certificate of analysis from the supplier of the water, we recommend that you qualify your facility by conducting appropriate tests at the point of use to verify that no other tests are necessary or that any additional tests you have chosen are sufficient to establish that the water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements or any contact surface, meets the requirements of final § 111.15(e)(2). We also recommend that you requalify your facility at the point of use at appropriate intervals.

If you use water from a private source, you must use water that complies with any State and local requirement and does not contaminate the dietary supplement. You may need to perform appropriate water treatment procedures, including filtration, sedimentation, and chlorination to satisfy final § 111.15(e)(2).

(Comment 94) Several comments would delete proposed § 111.15(d)(2), arguing that it is unnecessary to state a requirement that water meet the Environmental Protection Agency's NPDW standards. These comments state that if water is used in processing or at critical points in the cleaning process, then a manufacturer will already have established specifications for its appropriate use.

(Response) We agree that a manufacturer will need to establish specifications, under final § 111.70(a), for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement, and for water that is used in a manner such that the water may become a component of the dietary supplement. For reasons set forth in response to comment 88, final § 111.15(e)(2) establishes the minimum standards for water that will be used in a manner such that the water may become a component the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface. Thus, we disagree that proposed § 111.15(e)(2) be eliminated.

#### 6. Final § 111.15(f)

Final § 111.15(f) (proposed §111.15(e)) sets forth requirements for the plumbing of your physical plant.

Final § 111.15(f) requires your plumbing to be of an adequate size and design and be adequately installed and maintained to: (1) Carry sufficient

amounts of water to required locations throughout the physical plant; (2) properly convey sewage and liquid disposable waste from your physical plant; (3) avoid being a source of contamination to components, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition; (4) provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and (5) not allow backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary supplements, for cleaning contact surfaces, or for use in bathrooms and hand-washing facilities.

We did not receive comments specific to proposed § 111.15(e), other than comments arguing that certain text was unconstitutionally vague and arbitrary and capricious. We address those comments in section V of this document.

#### 7. Final § 111.15(g)

Final § 111.15(g) (proposed § 111.15(f)) sets forth requirements for sewage disposal and requires you to dispose of sewage into an adequate sewage system or through other adequate means.

We did not receive comments specific to proposed § 111.15(f).

#### 8. Final § 111.15(h)

Final § 111.15(h) (proposed § 111.15(g)(1)) sets forth requirements for the bathrooms of your physical plant. Final § 111.15(h) requires you to provide your employees with adequate, readily accessible bathrooms, and that the bathrooms be kept clean and not be a potential source of contamination to your components, dietary supplements, or contact surfaces.

(Comment 95) Several comments state companies should be given flexibility in designing their bathrooms. These comments assert the food CGMP requirements allow flexibility in bathroom design, so the dietary supplement CGMP rule should do the same. The comments would delete proposed § 111.15(g)(1) through (g)(3), which pertained to: (1) Keeping the bathrooms in good repair at all times; (2) providing self-closing doors; and (3) providing doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination, except where alternate means have been taken to protect against contamination.

(Response) We agree that it is unnecessary to require specific bathroom features such as those in proposed § 111.15(g)(1) through (g)(3) because you may be able to achieve compliance through other means better suited to your operations. Accordingly, we are revising the rule by deleting proposed § 111.15(g)(1) through (g)(3) as requested by the comments. However, we continue to believe that mechanisms such as self-closing doors and doors that do not open onto areas where components, dietary supplements, or contact surfaces are exposed to contamination will help protect against contamination.

#### 9. Final § 111.15(i)

Final § 111.15(i) (proposed § 111.5(h)) sets forth requirements for the hand-washing facilities of your physical plant. Final § 111.15(i) requires you to provide hand-washing facilities that are designed to ensure that an employee's hands are not a source of contamination of components, dietary supplements, or any contact surface, by providing facilities that are adequate, convenient, and furnish running water at a suitable temperature.

Final § 111.15(i) differs from the proposal in that the proposal would list six specific features of a hand-washing facility, such as effective hand-cleaning and sanitizing preparations (proposed § 111.15(h)(2)), air driers, sanitary towel service, or other suitable drying devices (proposed § 111.15(h)(3)), and trash bins that are constructed to protect against recontamination (proposed § 111.15(h)(4)).

(Comment 96) Several comments state we should give firms the flexibility to design their hand-washing facilities. According to these comments, substituting the word “may” for the word “must” would accomplish this. The comments argue that, as with bathrooms, an overall sanitation requirement should be sufficient, and that, as long as there is a strong and enforceable standard, firms should have the flexibility to adopt only those measures that are needed to meet the underlying requirement.

(Response) We agree that it is unnecessary to require specific hand-washing mechanisms because you may be able to achieve compliance through other means better suited to your operations. However, we disagree that an overall sanitation requirement would be sufficient, because such a requirement would not clearly state the purpose of the requirement, which is to ensure that an employee’s hands are not a source of contamination of components, dietary supplements, or any contact surface.

We are revising proposed § 111.15(h) (final § 111.15(i)) in the final rule in two respects. First, the final rule states that the hand-washing facilities are to be designed to ensure that an employee’s hands are not a source of contamination. Second, final § 111.15(i) states that the hand-washing facilities are to be adequate, convenient, and furnish running water at suitable

temperatures but does not provide the specific hand-washing mechanisms detailed in the 2003 CGMP Proposal.

#### 10. Final § 111.15(j)

Final § 111.15(j) (proposed § 111.15(i)) sets forth requirements for trash disposal at your physical plant. Final § 111.15(j) requires that you convey, store, and dispose of trash to: (1) Minimize the development of odors; (2) minimize the potential for trash to attract, harbor, or become a breeding place for pests; (3) protect against contamination of components, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and (4) control hazardous waste to prevent contamination of components, dietary supplements, and contact surfaces.

(Comment 97) One comment suggests deleting proposed § 111.15(i)(1) concerning minimizing the development of odors, because, the comment claimed, minimizing odors is not a “true” CGMP requirement.

(Response) We disagree that minimizing the development of odors is not part of CGMP. Odor from trash is often an indication of problems with microbial contamination, such as decomposition, decay, and the growth of harmful bacteria. In addition, odor from trash can attract pests. By conveying, storing, and disposing of trash to minimize the development of odors, you will help reduce the potential for problems with microbial contamination and pests.

#### 11. Final § 111.15(k)

Final § 111.15(k) (proposed § 111.15(j)) sets forth requirements for sanitation supervisors at your physical plant. Final § 111.15(k) requires that you assign one or more employees to supervise overall sanitation. Each supervisor must be qualified by education, training, or experience to develop and supervise sanitation procedures. Final § 111.15(k) differs from proposed

§ 111.15(j) in that the proposal would require that each supervisor be qualified by training and experience.

(Comment 98) Several comments suggest revising proposed § 111.15(j) to state that sanitation supervisors may be qualified by education, training, or experience (or any combination thereof) to develop and supervise sanitation procedures. In contrast, several comments say that sanitation supervisors should be qualified by both training and experience.

(Response) Consistent with our response to comment 76 in section VII of this document, final § 111.15(k) provides that sanitation supervisors, like other supervisors, must be qualified by education, training, or experience to develop and supervise sanitation procedures. As we also stated in response to comment 76, we acknowledge that some supervisory personnel may need a different range of education, training, or experience than others. However, we have decided to give firms the flexibility to decide the appropriate amount of education, training, or experience for a given job function. If that includes a combination of attributes, the firm should select and train employees accordingly.

*E. What Are the Requirements Under This Subpart for Written Procedures?*

*(Final § 111.16)*

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

We are adding a new final § 111.16 entitled “What Are the Requirements Under This Subpart for Written Procedures?,” to require you to establish and follow written procedures for fulfilling certain requirements of subpart C. You

must establish and follow written procedures for cleaning the physical plant and for pest control.

*F. What Design and Construction Requirements Apply to Your Physical Plant?*

*(Final § 111.20)*

Final § 111.20 addresses physical plant design and construction requirements.

1. Final § 111.20(a) and (b)

Final § 111.20(a) and (b) require that any physical plant that you use in the manufacturing, packaging, labeling, or holding of dietary supplements: (1) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations and (2) have adequate space for the orderly placement of equipment and holding of materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components and dietary supplements during manufacturing, packaging, labeling, or holding.

We did not receive comments specific to proposed § 111.20(a) or (b), other than comments arguing that certain text in proposed § 111.20(b) was unconstitutionally vague and arbitrary and capricious. We address those comments in this section and section V of this document.

2. Final § 111.20(c)

Final § 111.20(c) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide for the use of proper precautions to reduce the potential for mixups or contamination of components, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material.

Under final § 111.20(c) your physical plant must have, and you must use, separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components and dietary supplements during the following operations: (1) Receiving, identifying, holding, and withholding from use, components, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, labeling, or holding of dietary supplements; (2) separating, as necessary, components, dietary supplements, packaging, and labels that are to be used in manufacturing from components, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection; (3) separating the manufacturing, packaging, labeling, and holding of different product types including different types of dietary supplements and other foods, cosmetics, and pharmaceutical products; (4) performing laboratory analyses and holding laboratory supplies and samples; (5) cleaning and sanitizing contact surfaces; (6) packaging and label operations; and (7) holding components or dietary supplements.

(Comment 99) Several comments would change “computerized inventory controls” to “adequate inventory controls” in proposed § 111.20(c). The comments say that a requirement to use a computerized system is too prescriptive and that inventory controls that are not computerized may be equally effective in achieving compliance with proposed § 111.20(c).

(Response) These comments may have misinterpreted proposed § 111.20(c). Computerized inventory controls are an example of the type of system that may be appropriate; § 111.20(c) does not require you to have a

computerized system in the first instance. Thus, final § 111.20(c) continues to use computerized inventory controls as an example of a central system.

(Comment 100) Several comments ask us to clarify the degree of separation that is intended under proposed § 111.20(c) when it referred to “separate or defined areas” of a physical plant. These comments state that it is unclear if we expect a firm not to manufacture multiple products in a single room or area. The comments state that, if this is the case, this would be equivalent to the drug CGMP requirements and would be excessive. The comments argue that, if the proper controls are in place, manufacturing and packaging of multiple products is possible in a single room or area without compromising product identity, quality, strength, purity, and composition.

(Response) Final § 111.20(c) states that you must have and use separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation. The preamble of the 2003 CGMP Proposal explained that if your physical plant does not allow for physically separate areas, you could develop an alternative approach for segregating components and dietary supplements at points when they are received, stored, and rejected (68 FR 12157 at 12188). We interpret the comments as asking whether alternative approaches for segregating products could be used, even if physically separate areas were available in a facility, so that different materials could be processed in the same area. Final § 111.20(c) allows you to use “separate or defined areas of adequate size or other control systems;” thus, you can comply with this requirement by manufacturing multiple products in the same room or area instead of using a physically separate location, as long as you have systems in place to prevent contamination and mixups of components and dietary supplements.

## 3. Final § 111.20(d)

Final § 111.20(d) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements be designed and constructed in a manner that prevents contamination of components, dietary supplements, or contact surfaces.

Final § 111.20(d)(1) requires the design and construction to include: (1) Floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair; (2) fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage or condensate; (3) adequate ventilation or environmental control equipment, such as air flow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary supplements, or contact surfaces; (4) equipment that controls temperature and humidity, when such equipment is necessary to ensure the quality of the dietary supplement; and (5) aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary supplements, or contact surfaces with clothing or personal contact.

Final § 111.20(d)(1)(i) through (d)(1)(v) is similar to proposed § 111.20(d)(1), (d)(2), (d)(3), (d)(5), and (d)(6), respectively. Additionally, as explained in the following paragraphs, we have made other changes to proposed § 111.20(d)(1) (final § 111.20(d)(1)(i)) and proposed § 111.20(d)(5) (final § 111.20(d)(1)(iv)).

(Comment 101) Several comments argue that the requirement of proposed § 111.20(d)(1) that floors, walls, and ceilings be made of “smooth and hard surfaces,” if read literally, could be interpreted to prohibit the use of ceilings with drop-in tiles. These comments assert that, while there may be areas in a manufacturing plant where drop-in ceilings are inappropriate given the height of the ceiling, the nature of the product, or the type of operation conducted in that area, such ceilings are adequate in many areas of a manufacturing facility, and certainly are appropriate in places where product is labeled or stored. The comments argue that replacing such ceilings with surfaces that are “smooth and hard” is unnecessary. Several other comments argue that they could find no precedent in any food CGMP regulations for a provision specifying “smooth and hard surfaces” for ceilings, but did identify a precedent in the section of drug CGMP requirements relating to “aseptic processing.” The comments state that adopting such a drug CGMP requirement is inappropriate for dietary supplements.

The comments say the overall purpose of proposed § 111.20(d)(1) should be to ensure that facilities can be kept in a clean and sanitary condition. The comments would revise proposed § 111.20(d)(1) to require physical plants to have surfaces that can be adequately cleaned, but would give manufacturers the flexibility to use appropriate surfaces in different parts of a plant.

The comments also argue that the rule’s specificity establishes a conundrum for certain manufacturers to conform to other Federal regulations, e.g., Occupational Safety and Health Administration (OSHA) noise levels. The comments argue that firms should be allowed to simultaneously conform to both OSHA and FDA requirements.

(Response) We agree that a smooth and hard surface may not be necessary in every case to prevent contamination of the dietary supplement. However, you may need floors, walls, and ceilings that are constructed of smooth and hard surfaces to prevent contamination of the dietary supplement when, for example, physical attributes of components (e.g., particle size or electrostatic charge) would make it difficult to keep floors, walls, and ceilings clean. Consequently, we conclude that a requirement that the physical plant have floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair to prevent contamination of the dietary supplement is sufficient. We are revising final § 111.20(d)(1) to remove the language concerning smooth and hard surfaces. The final rule gives you the flexibility to determine how best to construct your facility in order to prevent contamination and to ensure the quality of the dietary supplements you manufacture, package, label, or hold.

Section 111.20(d)(1)(ii) of the final rule (proposed § 111.20(d)(2)) requires your physical plant design and construction to have fixtures, ducts, and pipes that do not contaminate components, dietary supplements, or contact surfaces by dripping or other leakage, or condensate. Final § 111.20(d)(1)(iii) (proposed § 111.20(d)(3)) pertains to adequate ventilation or environmental control equipment. We added “or other leakage” to clarify that the requirement relates to “leakage” regardless of whether the leakage is in the form of “dripping.”

(Comment 102) Proposed § 111.20(d)(5) would require your physical plant design and construction to include equipment that controls temperature and humidity. Several comments suggest adding a qualifier to the temperature and humidity control requirements so that controls are only required as necessary to prevent adulteration. The comments state there is adequate evidence that

temperature and humidity do not stimulate reproduction of microorganisms and pests in dietary supplements. The comments also argue that retesting older ingredients stored in an uncontrolled environment and subjected to heat, cold, and ambient humidity produced no evidence of reproduction of microorganisms. According to the comments, temperature and humidity may present issues with raw, unprocessed botanical ingredients or animal-derived ingredients, but there is no proven issue with the powdered botanical and animal derived ingredients used by the dietary supplement industry.

Several comments argue against requiring temperature and heat controls, asserting that most equipment used to manufacture dietary supplements is often cleaned with large amounts of hot water, and therefore temperature and humidity controls are not practical.

(Response) We agree that controls for temperature and humidity should only be required when necessary to ensure the quality of the dietary supplement, and we are revising final § 111.20(d) accordingly. However, we disagree that there is adequate evidence that temperature and humidity do not stimulate reproduction of microorganisms in dietary supplements. It is well-recognized that microorganisms such as bacteria will grow in a warm environment and that microorganisms, such as molds, will grow in a moist environment. In addition, if the comments are suggesting that this final rule should only include requirements that derive from specific, already known examples that the absence of a requirement directly led to a problem with a dietary supplement, we disagree. CGMP requirements can help prevent products from becoming adulterated during the manufacturing process, and, in certain cases, controlling temperature and humidity may be necessary to ensure the quality of the dietary supplement.

With respect to the comments stating that using hot water to clean equipment makes control of temperature and humidity impractical, we advise that a firm unable to control temperature and humidity in those parts of its facility where control is necessary to ensure the quality of the dietary supplement because it uses hot water to clean equipment would not be in compliance with final § 111.20(c). The provision requires that your physical plant have, and that you use, separate and defined areas of adequate size, or other control systems, to prevent contamination during operations such as cleaning contact surfaces (final § 111.20(c)(5)).

Final § 111.20(d)(2) (proposed § 111.20(d)(4)) requires that, when fans and other air-blowing equipment are used, such fans and equipment be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces.

(Comment 103) Several comments interpret proposed § 111.20(d)(4) as requiring fans and air-blowing equipment. These comments state this type of equipment is not always needed and may, in some instances, be more likely to cause adulteration than prevent it. The comments ask us to clarify that fans and other air-blowing equipment are only required when they are necessary to prevent adulteration.

(Response) Proposed § 111.20(d)(4) was intended to require that any fans and other air-blowing equipment you use be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary supplements, or contact surfaces.

Nevertheless, given the comments' misinterpretation, we are revising proposed § 111.20(d)(4) (final § 111.20(d)(2)) to state that, "When fans and

other air-blowing equipment are used,” those fans and equipment must be located and operated in a manner that minimizes the potential for contamination by microorganisms and particulate matter. This should clarify that the rule does not mandate the use of fans and air-blowing equipment.

(Comment 104) Some comments state that exhaust and venting equipment can, under certain circumstances, be a source of microbial contamination. The comments would revise proposed § 111.20(d)(4) to read: “Fans and other air-blowing or exhaust and venting equipment located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces.”

(Response) We decline to revise the rule as suggested by these comments as there is no need to do so. We consider exhaust equipment and venting equipment to be types of fans or air-blowing equipment and therefore covered by the term “fans and other air-blowing equipment.”

#### 4. Final § 111.20(e)

Final § 111.20(e) (proposed § 111.20(e)) requires that any physical plant that you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide adequate light in: (1) All areas where components or dietary supplements are examined, processed, or held; (2) all areas where contact surfaces are cleaned; and (3) hand-washing areas, dressing and locker rooms, and bathrooms.

We did not receive any comments specific to proposed § 111.20(e).

#### 5. Final § 111.20(f)

Final § 111.20(f) (proposed § 111.20(f)) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary

supplements use safety-type light bulbs, fixtures, skylights, or other glass or glass-like materials when the light bulbs, fixtures, skylights, or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation, unless your physical plant is otherwise constructed in a manner that will protect against contamination of components or dietary supplements in case of breakage of glass or glass-like materials.

We did not receive any comments specific to proposed § 111.20(f). On our own initiative, we are making clarifying changes to final § 111.20(f) by:

- Adding “or glass-like materials” after the word “glass.” Although proposed § 111.20(f) only specified glass, its intent was to cover any material that could shatter and contaminate components, dietary supplements, or contact surfaces. Therefore, we are adding glass-like material to final § 111.20(f) to cover fixtures and skylights that use non-glass materials (such as acrylic and polycarbonate materials) but could still contaminate components, dietary supplements, or contact surfaces if shattered or broken.

Further, we are stating that the requirement applies when the light bulbs, fixtures, skylights, or other glass or glass-like materials are suspended over exposed components or dietary supplements in any step of preparation. We made this change to prevent the rule from being misinterpreted as requiring firms to suspend light bulbs, fixtures, skylights, or other glass over components or dietary supplements in every step of preparation.

#### 6. Final § 111.20(g)

Final § 111.20(g) (proposed § 111.20(g)) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements provide effective protection against contamination of components and dietary supplements in bulk fermentation vessels. Such protection

includes: (1) Use of protective coverings; (2) placement in areas where you can eliminate harborages for pests over and around the vessels; (3) placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and (4) use of skimming equipment.

We did not receive comments specific to proposed § 111.20(g). We have made nonsubstantive, grammatical changes to the provision by replacing “by any effective means” with “effective” before the word protection and “including consideration of” with “by, for example:”.

#### 7. Final § 111.20(h)

Final § 111.20(h) (proposed § 111.20(h)) requires that any physical plant you use in the manufacturing, packaging, labeling, or holding of dietary supplements use adequate screening or other protection against pests, where necessary.

(Comment 105) One comment argues that proposed § 111.20(h) should be deleted because it is redundant when compared to proposed § 111.15(c) which would require you to not allow animals or pests in any area of your physical plant, except for guard or guide dogs in certain circumstances.

(Response) We disagree that final § 111.20(h) is redundant to proposed § 111.15(c) (final § 111.15(d)). Although both paragraphs deal with pests, final § 111.20(h) establishes a design requirement (i.e., a specific requirement to use adequate screening or other protection), while final § 111.15(d) sets forth a sanitation requirement (i.e., to not allow animals or pests in your physical plant). Therefore, we are retaining § 111.20(h) in the final rule.

*G. Under This Subpart, What Records Must You Make and Keep? (Final § 111.23)*

Final § 111.23(a) requires you to make and keep records required under this subpart in accordance with subpart P.

Final § 111.23(b) requires that you make and keep records of the written procedures for cleaning the physical plant and for pest control. This provision was added to ensure that the written procedures now required under final § 111.16 are maintained as required under subpart P.

Final § 111.23(c)(1) (proposed § 111.15(d)(3)) requires that you make and keep records that water, when used in a manner such that the water may become a component of the dietary supplement, meets the requirements of final § 111.15(e)(2).

(Comment 106) Several comments state there is no documentation requirement for water in the food or drug CGMPs. The comments, therefore, say there should be not be such a requirement in this final rule for dietary supplements.

(Response) To the extent that the comments assert we cannot include such a requirement for documentation in the dietary supplement CGMP because there is no corollary requirement in part 110, we have responded to this issue in section V of this document. The absence of a provision in drug CGMP requirements does not preclude us from requiring it in this final rule establishing CGMP requirements for dietary supplements for which we have no pre-approval scheme for ingredients used in such a product.

(Comment 107) Several comments ask us to clarify that, if a municipal water supply is used in a facility, the municipal water report is acceptable documentation of water quality. These comments say that a city's yearly report

of its municipal water quality should be sufficient documentation, and that independent testing should not be required. Several comments claim that our officials made statements to this effect during a public meeting held on May 6, 2003.

The comments also assert that water quality in a community is typically well known due to public notification that is required by the Environmental Protection Agency or due to other resources. These comments say that municipal water supplies are also well controlled as a result of Environmental Protection Agency regulations, and that, if water quality in a community or country is suspect, we can move aggressively to enforce the standards. The comments argue that, overall, our enforcement burden would be less than requiring every company in the industry to maintain and produce documentation related to water quality.

(Response) A yearly municipal report is a good starting point for documenting water meets the requirements of final § 111.15(e), however, such a report cannot stand on its own as the only assurance that the water of the regulated body (such as persons subject to this final rule) complies with these regulations. A municipal water report offers reasonable assurance that the water entering your plant satisfies the requirements of the Environmental Protection Agency's NPDW regulations. However, as discussed previously, the requirement to show that the water that is used in a manner such that the water may become a component of the dietary supplement, e.g., when such water contacts components, dietary supplements, or any contact surface, meets the requirements of § 111.15(e)(2), applies to water at the point of use, i.e., after it has passed through your plumbing system.

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

## IX. Comments on Requirements Related to Equipment and Utensils (Subpart D)

### A. Organization of Final Subpart D

Proposed subpart D contained two provisions regarding equipment, utensils, and automatic, mechanical, or electronic equipment. Table 5 of this document lists the sections in the final rule and identifies the corresponding sections in the 2003 CGMP Proposal that form the basis of the final rule.

TABLE 5.—DERIVATION OF SECTIONS IN SUBPART D

Final Rule	2003 CGMP Proposal
§ 111.25 What are the requirements under this subpart D for written procedures?	§ 111.25(c)(1) § 111.25(e)(1)
§ 111.27 What requirements apply to the equipment and utensils that you use?	§ 111.25(a), (b), (d), and (e)
§ 111.30 What requirements apply to automated, mechanical, or electronic equipment?	§ 111.30
§ 111.35 Under this subpart D, what records must you make and keep?	§§ 111.25(c)(1), (c)(2), (d), and (f), § 111.30(b)(2), (b)(5), and (c) § 111.50(c)(4)

## *B. Highlights of Changes to the Proposed Requirements for Equipment and Utensils*

### 1. Revisions

The final rule includes revisions that reflect the final rule applies to persons who manufacture, package, label, or hold dietary supplements unless subject to an exclusion in § 111.1.

### 2. Revisions Associated With the Reorganization

The revisions associated with the reorganization include:

- Renumbering proposed § 111.25 as final § 111.27 and correcting the numbering of the sections misnumbered in the 2003 CGMP Proposal;
- Requiring documentation and backup files in a separate section for recordkeeping requirements; and
- A nonsubstantive editorial change to refer to “automated equipment” rather than “automatic equipment.” Although there is no practical difference between these two terms, the term “automated” is the customary term.

### 3. Changes After Considering Comments

The final rule:

- Requires you to establish and follow written procedures to fulfill the requirements of subpart D, including written procedures for:
  - Calibrating instruments and controls;
  - Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and
  - Maintaining, cleaning, and sanitizing, as necessary, equipment, utensils, and other contact surfaces;
- Requires you to keep records of the maintenance, cleaning, and sanitizing of equipment either in equipment logs or in batch records;

- Requires that quality control personnel periodically review records of calibrations, inspections, or checks of automated, mechanical, or electronic equipment rather than approve such records when they are made;
- Specifies that software for a computer controlled process is included under automated, mechanical, or electronic equipment; and
- Clarifies that the requirement to retain backup files of software programs and of data entered into computer systems is for computer systems that you use in the manufacture, packaging, labeling, or holding of dietary supplements.

### *C. General Comments on Proposed Subpart D*

(Comment 108) Some comments claim one or more proposed requirements are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under § 706(2)(B) of the APA. These proposed requirements include:

- § 111.25(a)(1), which would require that equipment and utensils be “of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained”; and
- § 111.25(a)(2), which would require you to “use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components, dietary ingredients, or dietary supplements.”

In general, these comments assert the proposed sections did not define terms or phrases (such as “suitable” or “appropriate design”) in a way that persons who are subject to the rule can discern the meaning of the term. These comments also assert the proposed sections do not limit enforcement officers’ exercise of their discretion as to what will satisfy the requirements and, thus, invite exercise of unbridled discretion and disparate decisionmaking.

(Response) As discussed in section V of this document, we disagree that the terms are unconstitutionally vague, need to be defined, may result in discriminatory enforcement, or violate the APA. There has been sufficient usage of these terms in the food industry to enable manufacturers, and those who enforce the requirements, to comprehend and apply such terms. Agencies are permitted to use qualifying terms to enable them to address a wide variety of conditions at companies.

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

*(Final § 111.25)*

We received many comments that recommend written procedures for various provisions. We address the need for written procedures generally in section IV of this document. We also respond to comments on specific provisions in the same section. We are adding final § 111.25 that requires you to establish and follow written procedures for certain requirements.

*E. What Requirements Apply to the Equipment and Utensils That You Use?*

*(Final § 111.27)*

Final § 111.27 (proposed § 111.25) sets forth various requirements for equipment and utensils.

1. Final § 111.27(a)

a. *Final § 111.27(a)*. Final § 111.27(a) (proposed § 111.25(a)(1)) requires you to use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general

requirement has been broken out from the remaining requirements of final § 111.27(a).

Final § 111.27(a)(1)(i) through (a)(1)(v) provide examples of such equipment, such as equipment used to hold or convey (§ 111.27(a)(1)(i)), equipment using compressed air or gas (§ 111.27(a)(1)(iii)), and equipment used in automated, mechanical, or electronic systems (§ 111.27(a)(1)(v)).

Final § 111.27(a)(1) is similar to proposed § 111.25(a)(1) except for two, nonsubstantive editorial changes. The first change replaces “automatic equipment” with “automated equipment” in what is now § 111.27(a)(1)(v) (proposed § 111.25(a)(1)(5)). Although there is no practical difference between “automatic” and “automated,” the latter is the customary term.

(Comment 109) Some comments argue that the proposal’s use of terms such as “appropriate design, construction, and workmanship to enable them to be suitable for their intended use” and “adequately cleaned and properly maintained” are unconstitutionally vague under the Fifth Amendment and arbitrary and capricious under the APA.

(Response) We discuss those comments generally in section V of this document and, because we disagree that the final rule violates either the Fifth Amendment of the Constitution or the APA, we have not revised § 111.27(a)(1) except for the changes mentioned in the previous paragraphs..

b. *Final § 111.27(a)(2)*. Final § 111.27(a)(2) (proposed § 111.25(a)(2)) requires you to use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components or dietary supplements with: (1) Lubricants, (2) fuel, (3) coolants, (4) metal or glass fragments, (5) filth or any other extraneous material, (6) contaminated water, or (7) any other contaminants.

(Comment 110) Several comments state we should recognize that lubricants are an integral part of the encapsulation of gelatin-enrobed products and other dosage forms. These comments state lubricants are not potential contaminants, and in fact, help move gelatin ribbons through encapsulating machines. The comments would revise proposed § 111.25(a)(2) to read, “lubricants not intended for product contact,” to clarify the rule’s intent.

(Response) We decline to revise the final rule as suggested by the comments. Final § 111.27(a)(2) states that the use of equipment and utensils must not result in the contamination of components or dietary supplements with lubricants. If a lubricant used for encapsulation does not result in contamination of the components or dietary supplements then the encapsulating machine complies with final § 111.27(a)(2).

*c. Final § 111.27(a)(3).* Final § 111.27(a)(3) (proposed § 111.25(a)(3)) requires all equipment and utensils you use to be: (1) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces; (2) corrosion-resistant if the equipment or utensils contact components or dietary supplements; (3) made of nontoxic materials; (4) designed and constructed to withstand the environment in which they are used, the action of components or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and (5) maintained to protect components and dietary supplements from being contaminated by any source.

We did not receive comments specific to proposed § 111.25(a)(3). We have substituted the phrase “in which they are used” for “of their intended use” to make clear the requirement applies to equipment actually used in the manufacture, packaging, labeling, or holding of dietary supplements.

d. *Final § 111.27(a)(4)*. Final § 111.27(a)(4) (proposed § 111.25(a)(4)) requires that the equipment and utensils you use have seams that are smoothly bonded or maintained to minimize accumulation of dirt, filth, organic material, particles of components or dietary supplements, or any other extraneous materials or contaminants. Final § 111.27(a)(4) is similar to proposed § 111.25(a)(4) and is analogous to § 110.40(b) which requires that seams on food-contact surfaces be smoothly bonded or maintained so as to minimize accumulation of food particles, dirt, and organic matter and thus minimize the opportunity for growth of microorganisms. We have deleted the phrase “to minimize the opportunity for growth of microorganisms” as unnecessary in this context as the remaining wording of the provision encompasses this concept. In nonsubstantive editorial changes to final § 111.27(a)(4) we substitute “particles of components or dietary supplements” for “component or dietary supplement particles” to improve clarity, and re-order the list of extraneous materials or contaminants.

(Comment 111) Several comments argue that proposed § 111.25(a)(4) is overly restrictive by requiring equipment and utensils to “have seams that are smoothly bonded or maintained” to minimize contamination. The comments would revise the rule as follows: “Equipment and utensils you use must be of proper design and maintained to minimize accumulation \* \* \*.”

(Response) We disagree that proposed § 111.25(a)(4) (final § 111.27(a)(4)) is overly restrictive or that it requires a particular design. Final § 111.27(a)(4) requires seams that are smoothly bonded or maintained to minimize accumulation of dirt and gives firms the flexibility to use any design they choose, provided that the seams, by design or maintenance, minimize accumulation of contaminants.

e. *Final § 111.27(a)(5)*. Final § 111.27(a)(5) (proposed § 111.27(a)(5)) requires that each freezer, refrigerator, and other cold storage compartment you use to hold components or dietary supplements: (1) Be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that indicates, and records, or allows for recording by hand, the temperature accurately within the compartment and (2) have an automated device for regulating temperature or an automated alarm system to indicate a significant temperature change in a manual operation.

(Comment 112) The preamble to the 2003 CGMP Proposal invited comment as to whether we should require specific target temperatures for dietary ingredients or dietary supplements held in freezers or cold storage (68 FR 12157 at 12190). Several comments assert there is no need for us to specify storage temperatures for dietary ingredients or dietary supplements. The comments state most dietary supplements and dietary ingredients are shelf stable based on their low water activity control, which limits and slows chemical degradation and microbiological growth. Other comments say target temperatures are not required where freezing is used only to enhance the milling properties (fracturing) of dried botanicals and not to prevent microbial contamination.

(Response) We have not included any specific target temperature requirements in the final rule. Consequently, firms should determine for themselves what temperatures are needed to ensure that their dietary supplements are not adulterated (see final § 111.70 regarding the specifications you must establish).

f. *Final § 111.27(a)(6)*. Final § 111.27(a)(6) (proposed § 111.25(a)(6)) requires the instruments or controls you use in the manufacturing, packaging,

labeling, or holding of a dietary supplement, and instruments or controls that you use to measure, regulate, or record temperatures, pH,  $a_w$ , or other conditions, to control or prevent the growth of microorganisms or other contamination, be accurate and precise, adequately maintained, and adequate in number for their designated uses.

(Comment 113) One comment states that proposed § 111.25(a)(6)(i)'s requirements that instruments and controls be "accurate and precise" goes beyond "typical" calibration, and would require full validation of all instruments and controls. The comment argues that it is unnecessary to require both accuracy and precision for all instruments and controls, and would require precision only when necessary to prevent contamination. The comment states calibration to ensure accuracy of instruments and controls is usually sufficient to ensure control or prevention of the growth of microorganisms or other contaminants in most situations. The comment gives an example where thermometers are used to monitor temperature in a warehouse where dietary supplements are stored.

(Response) We disagree that proposed § 111.27(a)(6) requires full validation of all equipment and controls. As discussed in the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12190), accuracy means that the recorded measurements are equal to the (true value) of the thing being measured and precision means that individual measurements should be close to each other when made under the same conditions.

We also disagree that instruments need not be precise. An instrument that gives widely varying readings from one use to the next cannot ensure product quality over time. The degree of accuracy and precision is determined by the nature of the instrument or control and the process to which it relates. We

have, however, made several nonsubstantive, editorial changes to § 111.27(a)(6) as well as other edits to conform to changes made throughout the final rule.

These are the nonsubstantive editorial changes:

- Inserting a hyphen between “hydrogen” and “ion” and
- Revising the end of the paragraph so that it discusses “instruments and controls that you use \* \* \* to control or prevent the growth of microorganisms or other contamination \* \* \*.” The proposal stated “instruments and controls that you use \* \* \* that control or prevent the growth of microorganisms or other contamination \* \* \*”. (In other words, the final rule replaces “that” with “to”.)

*g. Final § 111.27(a)(7).* Final § 111.27(a)(7) (proposed § 111.25(a)(7)) requires that the compressed air or other gases you introduce mechanically into or onto a component, dietary supplement, or contact surface or you use to clean any contact surface be treated in such a way that the component, dietary supplement, or contact surface is not contaminated.

We received no comments specific to proposed § 111.25(a)(7).

## 2. Final § 111.27(b)

Final § 111.27(b) (proposed § 111.25(b)(1)) requires you to calibrate instruments and controls that you use in manufacturing or testing a component or dietary supplement. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general requirement has been broken out from the remaining requirements of final § 111.27(b) and now has paragraphs (b) and (b)(1) through (b)(3).

Final § 111.27(b)(1) through (b)(3) (proposed § 111.25(b)(1) and (b)(2)) requires you to calibrate before first use, and at the frequency specified in writing by the manufacturer of the instrument or control, or at routine

intervals, or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(Comment 114) Several comments object to the level of detail regarding the proposed calibration. Specifically, the comments object to requiring that manufacturers calibrate instruments and controls “as specified in writing by the manufacturer of the instrument and control.” The comments say this requirement is more prescriptive than drug CGMP requirements. The comments acknowledge that following manufacturer specifications is likely to be part of the calibration procedure, but state that firms should have the flexibility to modify their procedures as necessary. These comments would couple proposed § 111.25(b) with a requirement to establish and follow written procedures for calibrating instruments and controls and redraft proposed § 111.25(b) to mirror the drug CGMP requirements, using language such as “You must routinely calibrate instruments and controls that control or monitor critical parameters that you use in manufacturing or testing a component or dietary supplement.”

(Response) We disagree that proposed § 111.25(b) is overly prescriptive, exceeds drug CGMP requirements, or requires what is claimed by the comments. We discuss, generally, the issue of whether this final rule “exceeds drug CGMPs” in section V of this document. It is standard practice to calibrate an instrument before using it for the first time. A requirement that you calibrate as specified by the manufacturer of the equipment, or at routine intervals, or as otherwise necessary to ensure the accuracy and precision of the instrument and control, provides ample flexibility. Calibration, whether for instruments and controls used in manufacturing or testing drugs, devices, conventional foods, or dietary supplements, helps ensure the accuracy and precision of the

instrument and control. We do not prescribe how frequently such calibration must be done, but it must be done often enough to ensure that instruments and controls are operating within the correct parameters. We are revising the 2003 CGMP Proposal (at § 111.27(b)(2)) to clarify that the requirement relates to the frequency of calibration.

(Comment 115) Several comments claim requirements relating to calibration of instruments and controls should be limited to those instruments and controls that directly affect the identity, purity, quality, strength, and composition of a dietary supplement. According to the comments, in most manufacturing facilities, there are many instruments and controls that do not directly affect identity, purity, quality, strength, and composition, and that calibrating all instruments and controls could easily become unduly burdensome. The comments also would limit the requirement for periodic calibration of instruments and controls to those instruments and controls directly involved in the critical control parameters of the process, i.e., those parameters needed to meet specifications or to ensure identity, purity, quality, strength, and composition. The comments suggest that critical control parameters would have to be established.

(Response) We decline to revise the rule as suggested by the comments. The requirement to calibrate instruments and controls is limited to those instruments and controls that you use in testing a component or dietary supplement or in manufacturing a dietary supplement. Any such equipment has the potential to affect, directly or indirectly, the quality of the dietary supplement.

(Comment 116) Some comments would revise proposed § 111.25(b)(1) to state that “calibration should be done, where standards are available or where it is necessary to meet product specifications.”

(Response) We decline to revise the rule as suggested by the comments. It would be customary for an equipment manufacturer to have standards that can be used to calibrate the equipment, irrespective of the specific composition of the dietary supplement that is manufactured using that equipment. Equipment that is not or cannot be calibrated is unlikely to be in compliance with the requirement of final § 111.27(a)(6)(i) which requires instruments used in the manufacturing, packaging, labeling, and holding of dietary supplements, and instruments and controls that you use to perform certain operations, be accurate and precise.

(Comment 117) Some comments would revise proposed § 111.25 from the active voice to the passive voice. These comments claim that the active voice—i.e., requiring that “you” calibrate instruments and controls—requires that the dietary supplement manufacturer perform the calibration, when in fact such calibrations are often performed by an outside service.

(Response) You may use an outside service. We would not consider that calibration done for you by an outside service is any different than calibration done by your employees, and it is you (rather than an outside service) whom we will hold responsible to ensure that the calibration is performed. Accordingly, we decline to revise the provisions as suggested.

(Comment 118) Several comments say calibration before first use should not be required for certified, precalibrated instrumentation. The comments state precalibrated instrumentation is much more expensive than noncalibrated instrumentation, with the additional expense attributed to the precalibration.

Several comments would revise proposed § 111.25(b)(2) to read, “you must calibrate, or be able to verify that the calibration has been completed, before first use,” instead of “you must calibrate before first use.” The comments state that performance test results could be made available for this verification.

(Response) As written, the requirement that equipment be calibrated before first use includes calibration performed by a third party as a precalibration because we would consider that calibration performed by a third party as no different from calibration performed by one of your own employees. Under final § 111.35(b)(3) you must have documentation of the calibration.

If you purchase a precalibrated instrument, we strongly recommend that the vendor conduct the certification onsite after installation. If not, we strongly recommend that you verify that the instrument remains calibrated after it has been installed.

(Comment 119) Several comments ask whether the proposed requirement to calibrate “before first use” refers to the first use after installation or the first use after each start-up.

(Response) Final § 111.27(b)(1) refers to the first use after installation and does not require calibration after each start-up.

(Comment 120) Some comments would require that instruments and controls be calibrated, but argue that the final rule should not include detailed procedures specifying calibration methods. The comments said the rule should stay focused on end results and not process.

(Response) We disagree that the regulations should not focus on process. The essence of the CGMP requirements established by these regulations is a production and process control system, i.e., a process, that is designed to ensure the quality of the dietary supplement. The final rule gives firms the

flexibility to use different calibration methods as long as the method used is established in a written procedure.

### 3. Final § 111.27(c)

Final § 111.27(c) (proposed § 111.25(d)) requires that you repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

We received no comments specific to proposed § 111.25(d).

### 4. Final § 111.27(d)

Final § 111.27(d) (proposed § 111.25(e)) requires you to maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements. In order to correct the misnumbering of this provision in the 2003 CGMP Proposal, this general requirement has been broken out from the remaining requirements of final § 111.27(d) and now has paragraphs (d) and (d)(1) through (d)(7).

a. *Final § 111.27(d)(1)*. Final § 111.27(d)(1) requires that the equipment and utensils be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(Comment 121) Some comments argue that individual manufacturing operations will determine when sanitizing agents are needed after cleaning because of the wide variety of processes in the industry. The comments also say widespread use of sanitizing agents is creating resistant microbial strains, and incorporating unnecessary sanitization processes would contribute to this health concern.

Some comments recommend manufacturers calibrate sanitizing procedures to the particular process in a declared fashion depending upon the risk factors

of their process and materials. The comments set out several standards for sanitation procedures.

(Response) Final § 111.27(d) requires you to maintain, clean, and sanitize, as necessary, equipment, utensils, and any other contact surfaces, used to manufacture, package, label, or hold dietary supplements. The final rule thus gives you discretion to decide when sanitizers or sanitizing treatments, such as heat, are necessary and does not mandate the incorporation of unnecessary sanitization processes.

Additionally, under final § 111.27(d) you have flexibility to determine when sanitizing is appropriate and to sanitize only as necessary. We note that this flexibility was also present in proposed § 111.25(e)(1). Some comments suggested calibrating sanitation operations based on risk. The final rule largely leaves it up to firms to decide whether to sanitize or to just clean without sanitizing, based on the risks associated with the materials and process used. However, under final § 111.27(d)(3), if you use wet processing, if you determine that it is necessary to clean a contact surface, you must also sanitize that surface.

(Comment 122) Several comments state the final rule should include a requirement for validating cleaning procedures. The comments argue that testing requirements for finished dietary supplements might not test for certain contaminants that could arise as a result of cleaning. One comment asserts these potential contaminants would be discovered in a properly designed and executed cleaning validation protocol, and that including these written cleaning procedures in the final rule would help prevent adulteration and help ensure the identity, purity, quality, strength, and composition of dietary supplements.

(Response) We decline to require specific cleaning validation procedures in the final rule. Final § 111.27(d) and the requirements for written procedures under final § 111.25(c) are sufficient to ensure the use of cleaning procedures to ensure the quality of the dietary supplement.

b. *Final § 111.27(d)(2)*. Final § 111.27(d)(2) (proposed § 111.25(e)(2)) requires you to ensure that all contact surfaces, used for manufacturing or holding low-moisture components or dietary supplements, are in a dry and sanitary condition when in use. When the surfaces are wet-cleaned, you must sanitize them, when necessary, and allow them to dry thoroughly before you use them again.

We received no comments specific to proposed § 111.25(e)(2). We have substituted the phrase “when in use” for “at the time of use” for clarity.

c. *Final § 111.27(d)(3)*. Final § 111.27(d)(3) (proposed § 111.25(e)(3)) requires you, if you use wet processing during manufacturing, to clean and sanitize all contact surfaces, as necessary, to protect against the introduction of microorganisms into components or dietary supplements. Final § 111.27(d)(3) also requires that:

- When cleaning and sanitizing is necessary, you clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may become contaminated and
- If you use contact surfaces in a continuous production operation or in consecutive operations involving different batches of the same dietary supplement, you must adequately clean and sanitize the contact surfaces, as necessary. In this provision, we substituted “consecutive” for “back-to-back,” a nonsubstantive change. We also inserted “adequately” to make clear that cleaning and sanitizing must be adequate.

(Comment 123) Several comments argue against using the term “sanitize” in proposed § 111.25(e)(3). The comments state that, based on the proposed definition of “sanitize,” § 111.25(e)(3) would require evaluation of any sanitation steps to ensure that the level of log reduction is reached, for example, by taking “before and after” swab samples. The comments would revise proposed § 111.25(e)(3) to state that equipment, utensils, etc. shall be cleaned and sanitized in a manner that keeps microorganisms and other adulterants from contaminating all components, ingredients, in-process materials, and finished goods.

(Response) The final rule now defines “sanitize” as “to adequately treat cleaned equipment, containers, utensils, or any other cleaned product contact surface by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other microorganisms, but without adversely affecting the product or its safety for the consumer.” The definition no longer specifies a level of log reduction, so the revised definition should eliminate the comments’ concern as to any possible need for “before and after” samples.

d. *Final § 111.27(d)(4)*. Final § 111.27(d)(4) (proposed § 111.25(e)(4)) requires you to clean surfaces that do not come into direct contact with components or dietary supplements as frequently as necessary to protect against contamination. Final § 111.27(d)(4) relates to final § 111.27(d)(2) and (d)(3). For example, you would not have to clean your ceilings as often as you clean your contact surfaces because your ceilings normally do not touch components or dietary supplements. However, you would have to clean your ceilings as frequently as necessary to prevent dust or other contaminants from falling onto your components, dietary supplements, and contact surfaces.

We received no comments specific to proposed § 111.25(e)(4). We substituted “do not come into direct contact with” for “do not touch” as a nonsubstantive editorial revision.

e. *Final § 111.27(d)(5)*. Final § 111.27(d)(5) (proposed § 111.25(e)(5)) requires that single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) be: (1) Stored in appropriate containers and (2) handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary supplements, or any contact surface.

We received no comments specific to proposed § 111.25(e)(5).

f. *Final § 111.27(d)(6)*. Final § 111.27(d)(6) (proposed § 111.25(e)(6)) requires your cleaning compounds and sanitizing agents to be adequate for their intended use and safe under their conditions of use.

(Comment 124) One comment would delete proposed § 111.25(e)(6), stating it is redundant to proposed § 111.15(b), which would require you to use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use.

(Response) We disagree with this comment. Proposed §§ 111.15(b)(1) and 111.25(e)(6) (now final §§ 111.15(b)(1) and 111.27(d)(6), respectively) differed in their requirements and their applicability. Proposed § 111.15(b)(1) would apply to cleaning compounds and sanitizing agents used in the physical plant and would require them to be “safe and adequate under the conditions of use.” In contrast, proposed § 111.25(e)(6) would apply to cleaning compounds and sanitizing agents used on equipment, utensils, and contact surfaces used to manufacture, package, or hold components, dietary ingredients, or dietary supplements, and it would require such cleaning compounds or sanitizing

agents to be “adequate for intended use and safe under condition [sic] of use.” By using the phrase “adequate for intended use,” proposed § 111.25(e)(6) would have you consider whether a particular cleaning compound or sanitizing agent was appropriate for the particular use to which it was being applied.

Furthermore, depending on the situation, a cleaning compound or sanitizing agent that is appropriate for use on a physical plant may be inappropriate for use on equipment, utensils, and contact surfaces. For example, a powdered cleaning compound might be suitable for cleaning your physical plant’s floors, but inappropriate for cleaning equipment that mixes components. In other words, the “conditions of use” can also vary between final §§ 111.15(e)(1) and 111.27(d)(6) and lead to different conclusions regarding use of the same cleaning compound.

Additionally, on our own initiative, we have made two editorial, nonsubstantive changes to final § 111.27(d)(6). The final rule now states that the cleaning compounds and sanitizing agents must be adequate for “their” intended use and safe under “their conditions” of use.

*g. Final § 111.27(d)(7).* Final § 111.27(d)(7) (proposed § 111.25(e)(7)) requires you to store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and in a manner that protects them from contamination. We received no comments specific to proposed § 111.25(e)(7).

#### *F. Reorganization of Certain Paragraphs in Proposed § 111.25*

Proposed § 111.25 would impose certain requirements relating to written procedures for calibrating instruments and controls (proposed § 111.25(c) and (d)) and keeping calibration records (proposed § 111.25(f)). The final rule now

contains a new recordkeeping section (§ 111.35) that combines elements of proposed § 111.25(c), (d), and (f), as well as other sections. We discuss comments on proposed § 111.25(c), (d), and (f) and describe final § 111.35 in this section.

*G. What Requirements Apply to Automated, Mechanical, or Electronic Equipment? (Final § 111.30)*

Final § 111.30 sets forth requirements for automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement.

1. Comments on the Organization and Framework of Proposed § 111.30

(Comment 125) Some comments would revise proposed § 111.30(a) to replace “equipment to manufacture, package, label, and hold” with “equipment to manufacture, package, label, or hold.” The comments said that the same piece of equipment will not serve to manufacture, package, label, and hold components or dietary supplements.

(Response) We agree, and have revised § 111.30 accordingly. Final § 111.30 also contains the following changes:

- “Automatic” (as in “automatic equipment”) is replaced with “automated” as an editorial, nonsubstantive change;
- The phrase “determine the suitability of your equipment” has been revised to read “determine the suitability of the equipment \* \* \*” in § 111.30(b) and has no substantive impact; and
- We have substituted the word “met” for “achieved” to comply with “plain language” initiatives and to be consistent with other provisions.

We describe other changes to proposed § 111.30 in the following paragraphs.

(Comment 126) Several comments support proposed § 111.30 particularly with respect to computers. The comments state computers are susceptible to erroneous data input, are subject to malfunctions and software problems, and thus should be regulated under the final rule.

One comment questions why we organized proposed § 111.30 into two paragraphs (a) and (b). The comment claims there was no meaningful difference between the two paragraphs.

Other comments say some proposed requirements for automatic, mechanical, and electronic equipment, such as the proposed requirement for maintaining backup files of data entered into computer systems, would apply to automatic, mechanical, and electronic equipment that are not related to CGMPs. The comments argue that proposed § 111.30(b) would apply to computers on which payroll records are maintained, and that such a requirement does not belong in these CGMPs.

(Response) We agree, in part, and disagree, in part, with the comments. We agree that computers used in the manufacture, packaging, labeling, or holding of dietary supplements should be, and are, subject to final § 111.30.

We disagree, however, with those comments that interpreted proposed § 111.30(a) and (b) as being the same or interpreted proposed § 111.30 as applying to equipment that has no direct bearing on dietary supplements. Proposed § 111.30(a) differed from proposed § 111.30(b) in that paragraph (a) would pertain to the operation and suitability of your equipment within your manufacturing process. In contrast, proposed § 111.30(b) would apply to calibration of your equipment and controls you establish for your equipment.

We disagree with those comments that would interpret proposed § 111.30(b) as applying to payroll computers or other equipment that has no

CGMP function. To prevent misinterpretations of final § 111.30, we have revised it to apply to equipment “that you use to manufacture, package, label, or hold a dietary supplement” and renumbered proposed § 111.30(a)(1), (a)(2), (b)(1), (b)(3), and (b)(4) as § 111.30(a) through (e), respectively. Proposed § 111.30(b)(2) which would require you to make and keep written records of equipment calibrations, inspections, and checks, and proposed § 111.30(b)(5) which would require you to make and keep backup files of software programs and data, are now incorporated into final § 111.35, and we discuss these provisions later in this section.

(Comment 127) Several comments would limit proposed § 111.30(a) and (b) to automatic, mechanical, or electronic equipment that actually affects product specifications. The comments argue that, in a modern manufacturing facility, most, if not all, equipment used to manufacture, package, label, or hold any food product is automatic, mechanical, or electronic. The comments say that equipment, such as forklifts, should not be required to be designed or selected in a manner that ensures that product specifications are met, as would be required in proposed § 111.30(a)(1), or to be calibrated, as would be required in § 111.30(b)(1).

(Response) As we stated previously, we have revised § 111.30 so that it applies to equipment “that you use to manufacture, package, label, or hold a dietary supplement.” This revision should prevent the rule from being interpreted as applying to forklifts or other equipment that have no bearing on the manufacture, packaging, labeling, or holding of dietary supplements.

(Comment 128) Several comments argue that proposed § 111.30 is redundant to proposed § 111.25 and could be removed without meaningful effect. One comment argues that proposed § 111.30(a) and (b) (i.e., that all

automatic, mechanical, and electronic equipment be designed or selected to ensure that product specifications are consistently achieved and operate satisfactorily within operating limits required by the process) are redundant to proposed § 111.25(a)(1) (which would require that all equipment be of appropriate design, construction, and workmanship to enable them to be suitable for their intended use) and proposed § 111.25(a)(1)(v) (which would state that “equipment” includes automatic, mechanical, or electronic systems). The comment states that, for equipment to be suitable for its intended use, the equipment must operate satisfactorily within operating limits and, by extension, ensure that product specifications are consistently achieved. The comment states the separate regulations for automatic equipment in the drug CGMPs is less detailed despite our efforts to present the 2003 CGMP Proposal in “simplified language.”

(Response) We disagree that proposed § 111.30 is redundant to proposed § 111.25 (final § 111.27). Although both proposed §§ 111.25 and 111.30 pertained to equipment, they differed in their focus. Proposed § 111.25 would focus on equipment design, construction, maintenance, cleaning, sanitizing, and calibration. In contrast, proposed § 111.30 would focus on the equipment’s operation or suitability within your manufacturing process. For example, proposed § 111.30(a)(2) would require you to determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily “within the operating limits required by the process.” In contrast, proposed § 111.25 had no comparable suitability requirement insofar as your manufacturing processes were concerned. Thus, the proposed sections are not redundant, and the final rule retains both § 111.27 (proposed § 111.25) and § 111.30.

## 2. Comments Specific to Proposed § 111.30

a. *Final § 111.30(a) and (b)*. Final § 111.30(a) (proposed § 111.30(a)(1)) requires you, for any automated, mechanical, or electronic equipment you use to manufacture, package, label, or hold a dietary supplement, to design or select the equipment to ensure that dietary supplement specifications are consistently met.

Final § 111.30(b) (proposed § 111.30 (a)(2)) requires you, for any automated, mechanical, or electronic equipment that you use to manufacture, package, label, or hold a dietary supplement, to determine the suitability of the equipment by ensuring that the equipment is capable of operating satisfactorily within the operating limits required by the process.

(Comment 129) Some comments argue that the requirements of proposed § 111.30(a) might be impossible to meet because, in many instances, dietary supplement manufacturers cannot predict, at the time of purchase, the entire range of ingredients and products for which a particular piece of equipment might be used. The comments argue that a particular piece of equipment's suitability for a particular ingredient or product must be evaluated at the time the need arises. The comments would revise proposed § 111.30(a)(1). The words "Design and select equipment to ensure" would be replaced with the words "Use equipment that ensures;" and proposed § 111.30(a)(2) would be revised to replace the words "is capable of operating" with the word, "operates."

(Response) We disagree with the comments. Although a company may not know the entire range of products that a machine may be used for, proposed § 111.30(a)(1) and (a)(2) would neither require you to determine all uses of equipment at the time of purchase nor prevent you from evaluating an old

machine for a new use (these provisions are renumbered as final § 111.30(a) and (b), respectively). Thus, even if you chose to use old equipment for a new use, you still must select that equipment to ensure that dietary supplement specifications are consistently met with the new equipment use and determine the suitability of the new equipment use by ensuring that the equipment is capable of operating satisfactorily within the operating limits required by the new process.

(Comment 130) Several comments express concern that facilities and much equipment in the industry are old and lack historical documentation. These comments ask us to clarify whether manufacturers would have to establish baseline information for old facilities and equipment.

(Response) All equipment that you use, regardless of whether it is old or new, must be capable of doing what you intend it to do. Just as you could evaluate old equipment for a new use, you can demonstrate that old equipment does, in fact, do what you intend it to do for uses that you developed before these CGMP requirements were established, and thereby comply with final § 111.30(a) and (b).

(Comment 131) Several comments argue that our statement in the preamble to the 2003 CGMP Proposal that “systems need to be installed in a manner that takes into account the inherent limitations of the system, tested under conditions that reflect actual conditions of use” (68 FR 12157 at 12193) is vague and subject to multiple interpretations.

(Response) We disagree with the comment. The statement in question should be read in context because the preamble to the 2003 CGMP Proposal described several conditions for consideration. The preamble to the 2003 CGMP Proposal stated, in relevant part: “Some systems may work properly

only within a narrow range of environmental conditions, such as temperature and humidity, and some might be particularly sensitive to electromagnetic interference. The actual conditions of use of a system should be considered as early as possible in its design and development. Systems need to be installed in a manner that takes into account the inherent limitations of each system, tested under conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime” (68 FR 12157 at 12193.) Thus, suitability under final § 111.30(b) involves considerations of how the equipment would be affected by environmental conditions, whether the equipment is appropriate for its intended use, and whether the equipment can be maintained properly to ensure satisfactory operation.

(Comment 132) Several comments argue that the requirement of proposed § 111.30(a)(2) to “determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process” is vague and subject to many interpretations. These comments assert that this may cause an uneven playing field among companies as they apply differing standards to this requirement. The comments also argue that the vagueness of this requirement could potentially cause uneven enforcement, depending on the experience and understanding of individual inspectors.

(Response) We disagree that proposed § 111.30(a)(2) (final § 111.30(b)) is vague or may result in uneven enforcement. There has been sufficient common usage of terms such as “suitable,” “capable,” and “satisfactorily” in the industry to enable firms, and those who enforce the requirements, to comprehend and apply such terms to particular operations. Agencies may use

qualifying terms to enable them to address a wide variety of conditions, and such terms provide the flexibility needed for various operations.

(Comment 133) Several comments assert that proposed § 111.30(a)(2) is without justification and overly prescriptive when compared to conventional food CGMPs.

(Response) As discussed in section V of this document, the mere fact that a dietary supplement CGMP requirement has no counterpart in the food CGMP regulations, or has more detail than a counterpart in such regulations, does not mean that it is overly prescriptive. Rather, what is important is whether proposed § 111.30(a)(2) (final § 111.30(b)) is necessary to ensure the quality of the dietary supplements. For example, the preamble to the 2003 CGMP Proposal (68 FR 12157 at 12193) discussed how the incorporation of software into the operation of automatic equipment has both increased the complexity of such equipment and resulted in a process that may operate differently for each execution, because a software-based control system can be configured at will by the operator or by the system itself. Therefore, it is essential that you ensure that automated equipment is capable of operating satisfactorily within the operating limits required by the process.

(Comment 134) Several comments urge us to develop a separate guidance document with respect to determining the suitability and capability of equipment used in the manufacture of dietary supplements.

(Response) We believe that firms have sufficient experience to determine whether equipment is suitable and capable of performing its intended function. However, if we find that guidance will be helpful, we will consider whether to issue guidance at a later date.