> disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health, which would include a consumer complaint. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.

Communication about prices, package size or shape, or other matters that could not possibly reveal the existence of a hazard to health or do not concern the appearance, taste, odor, or quality of a dietary ingredient or a dietary supplement are not considered "consumer complaints" under the proposed rule. Consumer complaints related to an illness or injury related to a pharmacologically active substance of a dietary ingredient such as aristolochic acid would not be related to good manufacturing practices. The use of products containing aristolochic acid has resulted in several life-threatening adverse incidents.

Aristolochic acids are potent carcinogens and nephrotoxins that are present, primarily, in plants of the family Aristolochiaceae. A product that contains a large amount of it may result in the rapid onset of acute toxicity symptoms in a consumer using the product. A product containing a small amount could be used for years with no apparent adverse effects, until serious, irreversible effects, such as renal failure, has occurred. Such adverse effects are related to a pharmacologically active substance of a particular dietary ingredient, aristolochic acid. Thus, for the purpose of this regulation, a communication from a consumer that contains any allegation, written or oral, related to the safety of the use of a product because it contained a particular dietary ingredient, e.g., aristolochic acid would not be considered a "consumer complaint." We consider that a dietary supplement containing a dietary ingredient such as aristolochic acid, a substance that is nephrotoxic and carcinogenic, is adulterated under section 402(a)(1), (f)(1)(A), and (f)(1)(D) of the act.

Proposed § 111.3 defines "contact surface" as:

> * * * any surface that contacts a component, dietary ingredient, or dietary supplement, and those surfaces from which drainage onto the component, dietary ingredient, or dietary supplement, or onto surfaces that contact the component, dietary ingredient, or dietary

supplement ordinarily occurs during the normal course of operations.

Proposed § 111.3 gives some examples of contact surfaces, such as containers, utensils, tables, contact surfaces of equipment, and packaging. Under the proposed definition the term drainage includes both liquid and dry materials.

The proposed definition of "contact surface" is similar to the definition of "food-contact surface" in § 110.3(g), except we have used the terms "component, dietary ingredient, or dietary supplement" instead of food, and we have added several examples of contact surfaces. The proposed definition would include the inside of containers.

Proposed § 111.3 defines "ingredient" as "any substance that is used in the manufacture of a dietary ingredient or a dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement." The proposed definition would explain that an ingredient "includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the act." Thus, under proposed § 111.3, an "ingredient" may be a substance that is present in the finished dietary ingredient or dietary supplement that is intended to have some activity (such as a vitamin, mineral, or amino acid), but could also be a substance that is not intended to have any activity (such as the gelatin used to make the capsule holding the dietary

ingredients). This proposed definition and the proposed definition for "component" in proposed § 111.3 differ in that "component" includes the various materials used to manufacture a dietary supplement that may not appear in the final product.

Proposed § 111.3 defines "in-process material" as "any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary ingredient or dietary supplement." In-process material differs from a component because in-process material is created and used during manufacturing. For example, assume you manufacture a dietary supplement in hard tablet form. During the manufacturing process, you mix various ingredients, and you add binding agents and water to mix the ingredients thoroughly before making individual tablets. The mixture would be an "in-process material" because it is a blend or processed material that you will use to make your dietary supplement.

Proposed § 111.3 defines "lot" to mean:

> * * * a batch, or a specific identified portion of a batch intended to have uniform identity, purity, quality, strength, and composition; or, in the case of dietary ingredient or dietary supplement produced by continuous process, a specific identified

amount produced in a specified unit of time or quantity in a manner that is intended to have uniform identity, purity, quality, strength, and composition.

The proposed definition for "lot" is similar to the definition for "lot" in the proposed CGMP regulations for infant formula (61 FR 36154 at 36209, July 9, 1996), but would refer to "identity, purity, quality, strength, and composition" instead of "character and quality" to reflect the different characteristics of dietary ingredients and dietary supplements.

Proposed § 111.3 defines "microorganisms" as "yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern." The proposed definition would include, but would not be limited to, species that:

- Have public health significance;
- Could cause a component, dietary ingredient, or dietary supplement to decompose;
- Indicate that the component, dietary ingredient, or dietary supplement is contaminated with filth; or
- Otherwise may cause the component, dietary ingredient, or dietary supplement to be adulterated.

The definition of "microorganisms" includes microorganisms of public health concern and microorganisms that are of sanitary concern. Proposed § 111.3 is similar to the definition of

microorganism in § 110.3 but we added "sanitary concern" to the definition of microorganism. We added "sanitary" to clarify that we intend to include microorganisms of public health and sanitary concern. Although the term "sanitary" is not included in part 110, this change does not alter the generally recognized and scientific and legal meaning of the definition of "microorganism" in part 110, because part 110 is similarly concerned with sanitation. Under proposed § 111.3, E. coli O157:H7 would be a "microorganism" because it is a species that has public health significance. Other forms of E. coli, however, might not be of public health significance because not all forms of E. coli are pathogenic and present a public health risk. However, the presence of other forms of E. coli would be of sanitary concern.

One comment to the ANPRM objected to including viruses in a definition of "microorganisms" because it might imply that a manufacturer is able to demonstrate the absence of viral contamination in its dietary supplement.

We recognize that there are few effective virus detection methods and that the industry may be incapable of showing the presence or absence of specific viruses in its products. However, we have included viruses in the definition for "microorganisms" because animal tissues are used in the manufacture of dietary supplements, and the use of virus-containing tissue would adulterate the product. In order to

ensure that animal tissue that may be used in or as a dietary ingredient does not contain viruses of public health significance, certain precautions may be needed to be taken in procuring and handling such tissue. We discuss in section III.A.4 of this document what precautions we are seeking comment on that manufacturers take to prevent the use of tissue that may contain viruses of public health significance for dietary ingredient or dietary supplement manufacture or to prevent the introduction of such viruses into a dietary ingredient or a dietary supplement.

Proposed § 111.3 defines "must" to indicate that you have to comply with a particular requirement. "Must" is the plain language term that replaces "shall."

Proposed § 111.3 defines "pest" as "any objectionable insects or other animals including, but not limited to, birds, rodents, flies, mites, and larvae." Proposed § 111.3 is similar to § 110.3(j), although the proposed definition would add "mites" to the list of pests. We added mites to the definition of "pest" in this proposed rule because mites are capable of causing allergic reactions in persons who consume mite-contaminated foods (Ref. 44).

Proposed § 111.3 defines "physical plant" as "all or parts of a building or facility used for or in connection with manufacturing, packaging, or holding a dietary ingredient or a

dietary supplement." The proposed definition is similar to the definition of "plant" at § 110.3(k), except that we added the word "physical" before "plant" to distinguish between plants that are herbs, vegetables, and growing organisms, and buildings or facilities that are used in manufacturing, packaging, and holding a dietary ingredient or a dietary supplement. We also expanded the definition to cover the types of activities that would be subject to a CGMP rule for dietary ingredients and dietary supplements.

Proposed § 111.3 defines "quality control" as "a planned and systematic operation or procedure for preventing a dietary ingredient or dietary supplement from being adulterated." A planned and systematic operation or procedure provides a framework of current and effective methods and procedures for each dietary ingredient or dietary supplement you manufacture that will prevent dietary ingredients and dietary supplements from being adulterated. We discuss quality control in more detail later in this document.

Proposed § 111.3 defines "quality control unit" as "any person or group that you designate to be responsible for quality control operations." The quality control unit should consist of as many people as necessary to perform the quality control operations. Other provisions in this proposed rule address the

quality control unit's authority and responsibilities, and we discuss those provisions later in this document.

Proposed § 111.3 defines "representative sample" as "a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled." By stating that the "sample accurately portrays the material being sampled," we mean that it correctly represents and is typical of the material being sampled. It is important that the sample drawn accurately portrays the material being sampled because your analysis of the representative sample will be used to determine whether the material received is suitable for use in manufacturing or to determine that the dietary ingredient or dietary supplement is not adulterated and may be released for distribution. If the sample is not representative, you risk using a contaminated component or dietary ingredient in manufacturing and you may distribute an adulterated dietary ingredient or dietary supplement.

Proposed § 111.3 defines "reprocessing" as:

> * * * using, in the manufacture of a dietary ingredient or a dietary supplement, clean, unadulterated components, dietary ingredients, or dietary supplements that have been previously removed from manufacturing

> for reasons other than insanitary conditions and that have been made suitable for use in the manufacture of a dietary ingredient or dietary supplement.

The phrase "for reasons other than insanitary conditions" means that the component, dietary ingredient, or dietary supplement was removed from manufacturing because the incorrect amount of a component was added or other reason not due to insanitary conditions. However, the component, dietary ingredient, or dietary supplement that was removed from manufacturing because it became contaminated because of insanitary conditions, that is, it became contaminated with a microorganism of public health concern or a microorganism of sanitary concern, must not be reprocessed.

Proposed § 111.3 defines "sanitize" as:

> * * * to adequately treat equipment containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable

microorganisms, but without adversely affecting the product or its safety for the consumer.

One comment to the ANPRM pointed out that the industry-drafted outline's definition of sanitize differed from FDA's Food Code definition of sanitization (Ref. 45).

The FDA "Food Code" is a reference that guides retail outlets, such as restaurants and grocery stores and institutions such as nursing homes in how to prevent foodborne illnesses from food that is consumed without further processing by the consumer. Because dietary supplements also are consumed without further processing by the consumer, the FDA "Food Code" definition also is appropriate for use in sanitizing contact surfaces used in the manufacture of dietary ingredients and dietary supplements. The FDA "Food Code" definition of sanitization is to apply cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction of representative disease microorganisms of public health significance. Because dietary supplements are consumed without further processing, and for consistency with other agency definitions and standards, we are persuaded to propose the FDA "Food Code" definition of "sanitize." The agency believes that there may be a number of agents that can reduce the number of microorganisms present on

contact surfaces. A tolerable level of risk may be achieved by interventions that have been validated to achieve a cumulative 5-log reduction in the target pathogens. However, we do not specify the manner in which the risk is reduced. The proposed requirement mandates that you validate that the control measures are both appropriate to their operation and scientifically sound. In many cases, processors may rely on a written certification from the equipment manufacturer or may obtain a written scientific evaluation of a process, especially in cases where two or more control measures are used to accomplish the 5-log reduction in the target pathogen, to ensure that the process is adequate to destroy microorganisms of public health significance or to prevent their growth. The agency requests comments on its approach to pathogen reduction. In particular, the agency requests comments on whether all contact surfaces should be subject to proposed § 111.3 "sanitize."

Proposed § 111.3 defines "theoretical yield" as "the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production." We would complement this definition by defining "actual yield" in proposed § 111.3 as "the quantity that is actually produced at any appropriate step of manufacture or

packaging of a particular dietary ingredient or dietary supplement." Comparing theoretical yields to actual yields may help identify deviations or problems in the manufacturing or packaging process. To illustrate this point, you should understand that the theoretical yield is the quantity or amount that you expect to see at a particular step, while the actual yield is the quantity or amount that you actually obtain at a particular step.

Proposed § 111.3 defines "you" as "a person who manufactures, packages, or holds dietary ingredients or dietary supplements." "You" is the recommended "plain language" term designed to make regulations easier to understand. In this proposed rule, "you" refers to any person, within the meaning of section 201(e) of the act, who engages in any activity covered by this proposed rule. You should note that "you" includes, but is not limited to, the owner of the manufacturing firm as well as supervisors responsible for ensuring that these CGMPs are followed. In other words, "you" can be the person who owns the dietary ingredient or dietary supplement company as well as persons who work for the company.

Proposed § 111.3 defines "water activity" as "a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same

temperature." The proposed definition is consistent with the definition at § 110.3(r) and 21 CFR 113.5(w) and 114.5(h). Water activity can play an important role in promoting microbial growth, and that, in turn, can play a part in the contamination of your components, dietary ingredients, and dietary supplements.

Proposed § 111.3 defines "we" as meaning the U.S. Food and Drug Administration.

4. Do Other Statutory Provisions and Regulations Apply? (Proposed § 111.5)

Proposed § 111.5 would require that you comply with the regulations in proposed part 111, and with other applicable statutory provisions, and regulations under the act, related to manufacturing, packaging, or holding dietary ingredients or dietary supplements. Other statutory provisions or regulations that may apply to the manufacture, packaging, or holding of dietary ingredients or dietary supplements include, but are not limited to: (1) the PHS Act to prevent the introduction, transmission, or spread of communicable diseases; (2) part 110 ("Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food"); (3) part 113 (21 CFR part 113) ("Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers"); (4) part 123 (21 CFR part 123) ("Fish and Fishery Products"); (5) parts 70 through 82 (21 CFR parts 70 through 82) (for color additives); and (6) parts 170 through 189

(21 CFR parts 170 through 189) (for food additives). For example, a manufacturer who produces a dietary supplement that includes fish and fishery products, such as fish oil, would have to comply with HACCP regulations as required by part 123 as well as these CGMP provisions, if this rule is finalized, that apply to the dietary supplement. These other statutory provisions and regulations may apply because of the type of manufacturing process used or the type of ingredient in the dietary supplement.

Certain dietary ingredients, e.g., an animal-derived ingredient, may require certain manufacturing, packaging, and holding practices because, without such practices, they may pose serious public health and safety concerns related to the transmission of communicable disease. For purposes of this discussion, the term "animal-derived dietary ingredient" refers to materials, substances, tissues, body fluids, or body secretions from animals, birds, reptiles, insects, and other living creatures and substances that may be derived from them. We do not consider human tissues and other parts of humans, other than human milk, to be eligible to be a dietary ingredient under section 201(ff) of the act because such products have not been used as a "dietary substance for use by man to supplement the diet by increasing the total dietary intake" (21 U.S.C. 321(ff)(1)(E)).

Certain animal-derived dietary ingredients, as well as the handling practices associated with such ingredients, may pose serious public health and safety risks, and therefore, may require regulations. Animal-derived materials, substances, and tissues have the potential to cause serious illnesses or injuries when ingested. For example, bovine colostrum is a substance that is used in dietary supplements (Ref. 46). Bovine colostrum which is the lacteal secretion which precedes milk after a cow gives birth, likely presents the same potential health risks as does milk. Bovine milk may contain pathogenic organisms capable of causing diseases in man such as tuberculosis, undulant fever, and gastrointestinal disease (Ref. 47). Such milk must be pasteurized in accordance with 21 CFR 1240.61. We have proposed a specific requirement at § 111.65(c)(5) that would require that you sterilize, pasteurize, freeze, refrigerate, control hydrogen-ion concentration (pH), control humidity, control water activity, or use any other effective means to remove, destroy, or prevent the growth of microorganisms and to prevent decomposition. This requirement, which would apply to bovine colostrum for use in a dietary supplement, is necessary to remove certain potential health risks. Milk also may contain contaminants, such as drug residues if the cow has been treated with such substances prior to beginning lactation, that can cause serious adverse health effects in humans consuming the colostrum (Ref. 48). For

example, if the colostrum contains drug residues, a dietary supplement containing colostrum could cause an adverse effect in a person who is allergic to the drug residue. In addition, some dietary supplements contain raw brain tissue or glands (Ref. 49) that have a high risk of containing the infective agent that causes bovine spongiform encephalopathy (BSE) if they originate from an animal infected with the disease (Ref. 37). In fact, dietary ingredients derived from different wild and domesticated animals may present microbiological and contaminant hazards that are unique to animal-derived dietary ingredients simply because the ingredient may not be amenable to physical treatments (for example, sterilization to eliminate pathogens) or there may not be appropriate methods to identify or correct a potential risk (as in the case of BSE or other transmissible spongiform encephalopathies (TSEs)).

The PHS Act is intended to prevent the introduction, transmission, or spread of communicable diseases (42 U.S.C. 264). Dietary supplements may be regulated under the PHS Act to the extent necessary to prevent the introduction, transmission, or spread of communicable diseases in intrastate and interstate commerce. Dietary supplements that contain animal-derived ingredients may carry infective agents that may not be able to be identified or that may be resistant to inactivation, as described previously. We are not aware of dietary supplement

manufacturers' current procurement and handling practices of such dietary ingredients, nor the extent to which such dietary ingredients may be used. However, because the animal-derived dietary ingredients present important public health and safety issues, we are seeking comment on whether we should include in the final rule specific requirements for manufacturing, packaging, or holding animal-derived dietary ingredients. The U.S. Department of Agriculture (USDA) has imposed certain restrictions (see 9 CFR 94.18) on importation from certain regions of meat and edible products from certain animals. The USDA has determined that these regions present an undue risk of introducing BSE into the United States because BSE exists in the regions, because the regions have import requirements less restrictive than those that would be acceptable for import into the United States, and/or because of inadequate surveillance. Because there is no broadly applicable or validated diagnostic test available to manufacturers to identify BSE agent infected ruminant animals or BSE agent infected materials, the agency is considering whether to require, in our final rule, specific requirements under proposed § 111.35 that are designed to prevent the use of materials derived from certain animals from regions ("BSE Countries") identified in 9 CFR 94.18. Such requirements would likely include manufacturer procedures and records and supplier certifications to ensure that a component, dietary

ingredient, or dietary supplement is free of the agent of BSE. To prevent use of BSE agent-contaminated components, dietary ingredients, or dietary supplements, requirements for supplier certifications would likely include certification:

- Of the species of animal,
- Of the geographic origin of the animal,
- That no BSE was present in any of the animals in the herd from which the animal came and that none of the animals from the herd consumed mammalian-derived protein prohibited from use in ruminant feed,
- That any foreign manufacturer from which the material derived from animals was obtained:
    1. Did not co-mingle material derived from animals from BSE countries with material derived from animals from non-BSE countries,
    2. Established, validated, and followed plans or procedures to identify, track, and segregate material derived from animals from BSE countries from material derived from animals from non-BSE countries, and
    3. Used dedicated manufacturing operations to prevent co-mingling of materials derived from animals from BSE countries with materials derived from animals from non-BSE countries.

Manufacturers that rely on supplier certifications to ensure that materials derived from animals are BSE-free would likely need to verify the reliability of supplier certifications by conducting supplier audits at appropriate intervals. We invite comment on whether there are other requirements that should be considered by FDA for supplier certification or other manufacturing requirements to prevent the use of BSE agent-contaminated components, dietary ingredients, or dietary supplements. These specific requirements may be issued under the authority of the act or may need to be issued under PHS Act authority and may need to include relevant remedies available under the PHS Act. In addition, we invite comment on whether there are animal-derived materials from BSE countries that do not present a safety concern and, if so, whether FDA should consider exempting such materials from a possible requirement that would prevent the use of animal-derived materials from BSE countries in dietary supplements and why. The agency will consider whether to include, in the final rule, provisions specifically related to the manufacture, packaging, and holding of animal-derived dietary ingredients or dietary supplements. One of the more obvious and serious hazards is the transmission of TSE (Ref. 37). We have communicated with the public and manufacturers of FDA-regulated products about appropriate steps to increase product safety and minimize the risk of products contaminated with the BSE agent. We published a

notice in the FEDERAL REGISTER of August 29, 1994 (59 FR 44592), entitled "Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products" (Ref. 50). The notice, in part, published the November 1992 and December 1993 letters to manufacturers. In November 1992, we wrote to manufacturers of dietary supplements to alert them to the developing concern about TSEs in animals and Creutzfeldt-Jakob Disease in humans and recommended that they investigate the geographic source of any bovine and ovine material used in their products. We suggested that manufacturers develop plans to ensure, with a high degree of certainty, that bovine and ovine materials used in their products were not from BSE countries or from sheep flocks (foreign or domestic) infected with scrapie. In December 1993, we issued a letter recommending against the use of bovine-derived materials from cattle that resided in, or originated from, BSE countries in FDA-regulated products. In this letter, we recommended that manufacturers: (1) Identify bovine-derived materials in their products and identify all countries where the animals used to produce the materials had lived, (2) maintain traceable records for each lot of bovine materials and for each lot of FDA-regulated product using these materials, (3) document the country of origin of the live animal source of any bovine-derived materials used in the manufacture of the regulated products, and (4) maintain copies of the records identified above for FDA-

regulated products manufactured using bovine-derived materials at foreign sites or by foreign manufacturers. To assure the safety and suitability for human use of animal-derived biologics, our Center for Biologics Evaluation and Research (CBER) has developed guidances for industry that describe steps that manufacturers should take. For example, CBER guidances have recommendations that address viral safety, infections, disease risks, and BSE-risk reduction of biologic products that are animal-derived (see 63 FR 51074, September 24, 1998, and 63 FR 50244, September 21, 1998) (Refs. 51 and 52). Because we believe that the use of an animal-derived material, substance, or tissue in a dietary supplement raises many of the same serious public health and safety issues as animal-derived materials, substances, or tissues, in a biologic, we are considering whether the procedures that CBER recommends for a product with animal-derived materials, substances, or tissues would be appropriate for dietary ingredients and dietary supplements that contain animal-derived materials, substances, or tissues. We, therefore, invite comment on whether there should be specific CGMP requirements for the use of animal-derived materials, substances, or tissues in dietary ingredients and dietary supplements. We invite comment on these issues and specifically on whether there is a scientific basis for FDA to treat animal-derived dietary ingredients in a manner that is different from, or that would offer less protection than,

what is recommended for animal-derived biologics when the same public health and safety risks are present. We also invite comment on our legal authority with respect to these issues.

5. Exclusions (Proposed § 111.6)

Proposed § 111.6 would state that these CGMP regulations do not apply to a person engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons. This proposed exclusion is similar to the exclusion in § 110.19 for raw agricultural commodities. Accordingly, persons who engage in such activities related to raw agricultural commodities (which are defined in section 201(r) of the act), although not subject to these proposed CGMP regulations under section 402(g) of the act, would continue to be subject to other adulteration provisions in section 402 of the act.

We recognize that including in the proposed rule persons who engage in the activities related to the harvesting, storage, or distribution of such commodities, as described previously, could reduce the risk of microbial contamination in dietary ingredients and dietary supplements. Nevertheless, the proposal does not contain requirements for persons handling such commodities before distribution to a dietary ingredient or dietary supplement manufacturer because the scientific basis for reducing or

eliminating pathogens in various settings is evolving. We invite comments on whether we should include provisions in the CGMP proposal that would include persons who handle raw agricultural commodities.

Even though the proposed rule would not cover persons who harvest or otherwise handle raw agricultural commodities before distribution of these commodities to a dietary ingredient or dietary supplement manufacturer, we recommend some practices to help you minimize microbial food safety hazards in such commodities that you may use in a dietary ingredient or dietary supplement. We recommend that you adapt, to your practices, the good agricultural practices (GAPs) and good manufacturing practices for fruits and vegetables that we issued as a guidance document: "Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables" (Ref. 53). This guidance document includes recommended GAPs for water, worker health and hygiene, sanitary facilities, field sanitation, packing, and transportation. Those who harvest, store, or distribute raw agricultural commodities for incorporation into dietary ingredients or dietary supplements should adapt these practices to their specific operations.

B. Personnel (Proposed Subpart B)

Proposed subpart B contains three provisions dealing with personnel matters. In general, the proposed provisions are similar to the current CGMP requirements for food personnel in § 110.10.

1. What Microbial Contamination and Hygiene Requirements Apply? (Proposed § 111.10)

Individuals who handle components or dietary supplements may affect the purity or quality of those components or dietary supplements if they fail to take precautions to guard against microbial contamination or other types of contamination. For example, an employee who has an illness could unintentionally transfer bacteria or viruses causing such illness to a dietary supplement by simply handling the dietary supplement.

Proposed § 111.10(a), therefore, would require that you take measures to exclude from any operations any person who might be a source of microbial contamination of any material including components, dietary ingredients, dietary supplements, or contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. We based proposed § 111.10(a) on similar requirements in § 110.10.

Proposed § 111.10(a)(1) would require that you exclude any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion (such

as a boil, sore, or an infected wound), or any other abnormal source of microbial contamination from any operations, which may be expected to result in microbial contamination of components, dietary ingredients, dietary supplements, or contact surfaces, from working in any operations until the condition is corrected. For example, if an employee tells you that his or her physician has diagnosed that the employee has a fever, and the employee normally handles your dietary supplements, you must take steps to ensure that the employee does not come into contact with your dietary supplements because the fever may suggest that the employee has an infection and there is a reasonable possibility of contamination. Likewise, if your supervisors see that an employee has an open wound or sore, and the employee normally handles dietary ingredients, you must take steps to ensure that he or she is excluded from handling dietary ingredients because the open wound or sore could be a source of microbial contamination and because there is a reasonable possibility of contamination.

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

Proposed § 111.10(b) would apply if you work in operations where adulteration of components, dietary ingredients, dietary supplements, or contact surfaces may occur. The proposal would require that you use hygienic practices to the extent necessary to protect against contamination of those components, dietary ingredients, dietary supplements, or contact surfaces.

These hygienic practices would include, but would not be limited to:

- Wearing outer garments in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface. Outer garments may include gowns or aprons;
- Maintaining adequate personal cleanliness;
- Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:
  1. Before starting work;
     After each absence from the work station; and
  2. At any other time when hands may become soiled or contaminated. Hands may become soiled or contaminated after meals or after using the bathroom;
- Removing all unsecured jewelry and other objects that might fall into components, dietary ingredients,

dietary supplements, equipment, or packaging, and removing hand jewelry that cannot be adequately sanitized during periods when you manipulate components, dietary ingredients, or dietary supplements by hand. If the hand jewelry cannot be removed, the proposal would require that it be covered by material that is intact, clean, and in sanitary condition that effectively protects against contamination of your components, dietary ingredients, or dietary supplements, or contact surfaces.

- Maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition;
- Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other hair restraints;
- Not storing clothing or other personal belongings in areas where components, dietary ingredients, dietary supplements, or any contact surfaces are exposed or where contact surfaces are washed;
- Not eating food, chewing gum, drinking beverages, and using tobacco products in areas where components, dietary ingredients, dietary supplements, or any

contact surfaces are exposed or where contact surfaces are washed; and

- Taking any other necessary precautions to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces by microorganisms, filth, or other extraneous materials, including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

Each of these procedures is necessary because good personal hygiene should help prevent contamination from microbial sources (such as bacteria) as well as from nonmicrobial sources (such as dirt and hair).

We seek comment on whether we should require, in a final rule, that you establish and follow written procedures to ensure that you comply with the requirements of that section. We believe that any such written procedures should describe, in sufficient detail, the measures you take to ensure that no one is a source of microbial or other contamination and the measures you take to ensure that no one contaminates any material, including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. An example of a written procedure would be a procedure for developing and

implementing a training program on hygienic practices in the workplace. As stated previously, we invite comment on whether such written procedures should be required in a final rule, and whether there are other procedures, that we should include in a final rule.

A comment to the ANPRM stated that any requirements on disease control should be limited to manufacturing, processing, and handling of raw agricultural material and are not appropriate for manufacturing dietary supplements derived from chemicals. The comment stated that chemical processes are carried out in closed pipes and vessels, so the risk for human contamination is very low. The comment, therefore, said that FDA should allow workers who have wounds to continue working in manufacturing operations.

We disagree that the regulations on disease control should be limited to manufacturing, processing, and handling raw agricultural material. Because contamination may occur at any time during manufacturing, packaging, or holding operations, requirements concerning disease control must apply to all operations where a person may contaminate a component, dietary ingredient, dietary supplement, or contact surface. For example, an employee could contaminate a dietary supplement (of agricultural origin or synthetic origin) or contact surface during packaging operations. However, if we adopted the

comment's suggested limitation, contamination of a synthetic dietary supplement could occur, and there would be no regulatory requirement to guard against such contamination.

As for employees with open wounds, proposed § 111.10(a) would require that you exclude a person with an open lesion or any other abnormal source of microbial contamination from any operation which may adulterate the component, dietary ingredient, dietary supplement, or contact surface. Whether the proposed rule would require that you exclude a person with an open lesion or another abnormal source of microbial contamination from working in a closed system area, such as when the product is contained completely in closed pipes or vessels, would depend on whether, as a result of exposure, there would be a reasonable possibility of the component, dietary ingredient, dietary supplement, or contact surface becoming contaminated. Thus, when a dietary ingredient or dietary supplement is manufactured in a completely closed system, this proposed requirement on open lesions might not apply if there is no reasonable possibility of contamination. However, you must take the measures that would be required by § 111.10(a) if there is a reasonable possibility that any person might cause contamination of components, dietary ingredient, dietary supplements, or contact surfaces.

Comments to the personnel provisions, and other provisions, stated that the industry-drafted outline used phrases such as

"includes, but are not limited to," when giving examples of how to comply with various requirements. The comments suggested that this phrase be changed to "may include" to clarify that items that follow the phrase are simply examples of how to comply with a particular requirement and are not binding or do not represent an exhaustive list of examples.

We decline to draft the proposal as suggested by the comments because we do not agree that when we state "includes, but are not limited to," we are providing examples of how to comply with the regulations. When we state that a regulation requires a manufacturer, packager, or holder to establish certain practices which "includes, but is not limited to" a list of procedures or activities, we are stating that compliance with the regulation requires that you adopt, at the minimum, the procedures or activities listed in the regulation. Therefore, when we state "includes, but is not limited to," we mean that the list of procedures or activities following the "includes" statement is a list of requirements.

2. What Personnel Qualification Requirements Apply? (Proposed § 111.12)

Proposed § 111.12 would establish basic qualification requirements for employees. Proposed § 111.12(a)(1) would require that you have qualified employees to manufacture, package, or hold dietary ingredients or dietary supplements. We

are not proposing a general standard for determining how many employees are necessary, but there should be enough to manufacture, package, or hold dietary ingredients or dietary supplements consistent with these proposed CGMPs. A one-person operation is not precluded provided that one person is sufficient to achieve, maintain, and document CGMPs. However, general manufacturing practice suggests the need for a minimum of two persons, the first to perform the work and a second person to check the work performed to ensure that a manufacturing deviation or an unanticipated occurrence is not overlooked. Furthermore, such oversight may be cost effective in preventing product recalls necessary because a deviation or unanticipated occurrence was not detected and reviewed before the product distribution. However, we leave the determination of the actual number of employees necessary to your discretion. As stated previously, we invite comment on whether there is a minimum number of employees needed to manufacture dietary ingredients or dietary supplements.

Proposed § 111.12(a)(2) would require that each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties. Training is necessary to ensure that employees know how to correctly and fully perform the operations in question and to ensure that the employees are competent to produce an unadulterated product. The extent and frequency of the training is left to the

manufacturer's discretion. The extent and frequency of training needed for your employees will depend on the scope of the employee's activities and experience. For example, training may be necessary when you hire new employees, when employees engage in new activities, when your physical plant implements new manufacturing practices, or when you add new equipment or new processes to manufacturing. For example, an employee responsible for measuring ingredients during batch production should have sufficient training or expertise to perform those functions. If that employee does not know how to measure correctly, the employee may add too much of an active ingredient, which may cause the product to be adulterated. Thus, proposed § 111.12 would establish requirements for your employees.

We invite comment on whether we should require, in a final rule, a requirement that you document and keep records regarding each employee's training. We believe that the records, if required, should show the content and date of the training. Such records may be useful in determining whether an employee has received the training necessary to perform his or her duties. We invite comment on not only whether such records should be required in a final rule, but also what types of information such records should contain.

You may use consultants to advise you on any aspect of the manufacture, packaging, or holding of dietary ingredients or

dietary supplements. Any consultant you use should be qualified by training and experience to provide the advice they give to you. We invite comment on whether we should require, in a final rule, that you document each consultant's name, address, and qualifications and include a description of the services that the consultant provided. Such records may assist you in knowing who to contact and where to contact him or her if questions arise concerning the advice given.

A comment to the ANPRM suggested that the employee qualification requirements in the industry outline should, in part, state that "proper education, training, *or* experience" is required instead of "proper education, training, *and* experience" is required (emphasis added).

We disagree with the use of "or" instead of "and." We omitted the term "proper education" because "training" may be considered a form of "education." However, the proposed rule uses the conjunction "and" because, while some might consider "experience" to be a form of "training," most consider "experience" to be knowledge that a person gains over time as he or she becomes increasingly familiar with a particular action or piece of equipment.

Training, however, may not just include on-the-job training, but may include some type of educational experience derived from attending classes or lectures or some other formal instruction on

a particular subject. Some positions not only require the employee to have experience or training on the job, but also require that the employee have the appropriate educational background, for example, to understand the significance of using a particular test method or understanding the significance of a processing deviation and how to respond to such deviation. The word "and" includes situations where on-the-job training may be adequate and also situations where educational training may be required. Therefore, proposed § 111.12(a)(2) refers to "training and experience."

3. What Supervisor Requirements Apply? (Proposed § 111.13)

Proposed § 111.13 would establish general supervision requirements and is similar to a provision that appeared in the industry-drafted outline. Proposed § 111.13(a) would require that you clearly assign to qualified supervisory personnel the responsibility for ensuring that all CGMP requirements in part 111 are met. You should assign an adequate number of qualified personnel to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements. We are not proposing a general standard for determining how many supervisors are necessary and a one-person operation is not precluded provided that one person is sufficient to supervise CGMPs. As stated previously, we invite comment on whether there is a minimum number of qualified personnel to supervise the

manufacturing, packaging, or holding of dietary ingredients or dietary supplements. Proposed § 111.13(b) would require you and your supervisors to be qualified by training and experience to supervise.

Making supervisors responsible for compliance with the regulations would be an important step in manufacturing, packaging, and holding dietary ingredients and dietary supplements under conditions that will not cause adulteration and misbranding. We believe that clearly designating compliance responsibilities to individuals increases the likelihood of compliance with the regulations.

One comment to the ANPRM questioned why supervisory personnel must be "qualified" when the food CGMP regulations require supervisory personnel to be "competent" (see § 110.10(d)).

We consider the terms to be equivalent in this case. The Webster's II New Riverside University Dictionary defines competent as "able to perform as required: competent" and further defines "qualified" as "having met the requirements for a specific position or task" (Ref. 54). Therefore, we consider the words "qualified" and "competent" in proposed § 111.13 and § 110.10(d), respectively, should be considered synonymous.

Another comment to the ANPRM questioned making supervisors responsible for ensuring compliance by all personnel with all

CGMP requirements. The comment stated that absolute compliance with each and every CGMP requirement cannot be ensured, but that requiring a supervisor to be responsible may make the supervisor personally liable in the event of noncompliance.

Proposed § 111.13(a) would require that manufacturers assign responsibility to qualified supervisory personnel. Doing so will help ensure that the CGMPs are followed. In general, if the proposed rule is finalized, manufacturers, packagers, and holders would be responsible for complying with these CGMP requirements and for ensuring that they assign responsibility to qualified supervisors. We consider many factors when we take enforcement action, and so the facts surrounding a CGMP violation will influence the type of enforcement action we take. The manufacturer is responsible under § 111.13(a) for ensuring that qualified supervisory personnel are assigned to oversee the implementation of these CGMPs.

C. Physical Plant (Proposed Subpart C)

Proposed subpart C consists of provisions intended to help prevent contamination from your physical plant. These provisions are similar to the food CGMP requirements found in §§ 110.20, 110.35, and 110.37 which pertain to buildings and facilities.

We have not proposed 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, dietary ingredients, or dietary supplements. We invite comment on whether such requirements should be included in a final rule. Section § 110.20(a), identifies several methods necessary for adequate ground maintenance, such as:

- Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of your physical plant so that it does not attract pests, harbor pests, or be used by pests for breeding;
- Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where food is exposed;
- Adequately draining areas that may contribute to the contamination to food by seepage, filth, other extraneous materials, or by providing a breeding place for pests; and
- Adequately operating systems for waste treatment and disposal in an adequate manner so that they do not constitute a source of contamination in areas where food is exposed.

For example, rodents, insects, and other pests may be attracted to garbage, and if you do not take adequate steps to remove or dispose of garbage, you may be risking contamination from those

rodents, insects, or other pests. Rodents, insects, and other pests are sources of feces, hair, and other potential contaminants (Refs. 55 and 56). We invite comment on whether we should require, in a final rule, that you take these steps and/or other steps to protect against contamination.

1. What Sanitation Requirements Apply to Your Physical Plant? (Proposed § 111.15)

Proposed § 111.15(a), like § 110.35(a), would require that you keep your physical plant in a clean and sanitary condition and in sufficient repair to prevent contamination of components, dietary ingredients, dietary supplements, or contact surfaces. For example, holes in your physical plant's walls or windows could allow pests or contaminants to enter, so proposed § 111.15(a) would require that you repair those holes.

Proposed § 111.15(b) pertains to cleaning compounds, sanitizing agents, and pesticides you use. The proposal is similar to § 110.35(b) and, in essence, would require that you use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and are safe and adequate under the conditions of use. By saying that the cleaning compounds and sanitizing agents should be "free from microorganisms," we mean that your use of those cleaning compounds and sanitizing agents should not contaminate your components, dietary ingredients, dietary supplements, or contact

surfaces with microorganisms. We are proposing this requirement because microorganisms, if present in your cleaning compounds or sanitizing agents, can contaminate your contact surfaces or deactivate the sanitizing agent and, as a result, adulterate your components, dietary ingredients, dietary supplements, or contact surfaces. We advise that you should verify that cleaning compounds and sanitizing agents are free from contamination by microorganisms of public health significance and are safe and adequate under their conditions of use. Such verification may include buying these substances under a supplier's guarantee or certification or you may examine them for contamination.

Several comments on the industry outline published in the ANPRM objected to the idea 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." The comments stated that such language is unnecessary and may be interpreted as too restrictive and that manufacturers should be able to determine the appropriate means of assuring compliance.

We agree with the comments that you may determine the appropriate means of assuring compliance with this regulation. The proposed rule would not require that you follow any particular method for assuring compliance; instead, the proposal would give you the flexibility to decide how to ensure that your

cleaning compounds and sanitizing agents are free from contamination and are safe and adequate under the conditions of use.

Proposed § 111.15(b)(2) would require that you not use or hold toxic materials in a physical plant in which contact surfaces, components, dietary ingredients or dietary supplements are manufactured or exposed, unless those toxic materials are necessary:

- To maintain clean and sanitary conditions,
- For use in laboratory testing procedures,
- For maintaining or operating the physical plant or equipment, or
- For use in the physical plant's operations.

If at least one of the listed conditions is not met, you must not use or hold the toxic material because there would be no reason to risk contamination from exposure to such material if it is not necessary to your operations.

Proposed § 111.15(b)(3) would require that you identify and hold toxic cleaning compounds, sanitizing agents, pesticides, and pesticide chemicals in a manner that protects against contamination of components, dietary ingredients, dietary supplements, and contact surfaces. You must take steps to store your toxic materials in a way that prevents them from contaminating your dietary ingredients and dietary supplements.

If such products were stored in manufacturing areas or where dietary ingredients or dietary supplements may be otherwise exposed to such products, those toxic materials may come in contact with the dietary ingredients or dietary supplements and thereby contaminate them. In addition, clearly identifying the containers in which such toxic materials are held will prevent accidental use.

One comment to the ANPRM objected to the provision in the industry outline that would require manufacturers to register and use rodenticides, insecticides, and fungicides in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act and to follow all relevant Federal, State, and local government requirements. The comment said the requirement would be redundant with other regulations.

Although this CGMP proposed rule does not propose a requirement that you follow all relevant Federal, State, and local government requirements when applying, using, or holding toxic cleaning compounds, sanitizing agents, and pesticides, the proposed rule does not relieve you from such obligations.

Proposed § 111.15(c) pertains to pests. Proposed § 111.15(c)(1) would require that you exclude animals or pests from all areas of your physical plant, while proposed § 111.15(c)(2) would require that you take effective measures to exclude pests from your physical plant and to protect against the

contamination of components, dietary ingredients, dietary supplements, or contact surfaces. Therefore, if you have pests in your physical plant, you must take immediate action to get rid of them. In addition, you must take measures to prevent those and any other type of pests from entering your physical plant.

You should note that, like § 110.35(d), proposed § 111.15(c)(1) would allow guard dogs and guide dogs in your physical plant if their presence will not result in the contamination of components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed § 111.15(c)(3) would require that you not use insecticides, fumigants, fungicides, or rodenticides unless you take precautions to protect against contamination of your components, dietary ingredients, dietary supplements, or contact surfaces. For example, some pesticides may cause adverse effects in humans, so you must take precautions to ensure that any pesticides you use will not contaminate your components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed § 111.15(d) would apply to water supplies and is patterned after the food CGMP requirement at § 110.37(a). 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:

- Manufacturing dietary ingredients or dietary supplements;
- Making ice that comes into contact with components, dietary ingredients, dietary supplements, or contact surfaces;
- Cleaning surfaces; and
- 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 surfaces, at a minimum, comply with the National Primary Drinking Water (NPDW) regulations prescribed by the Environmental Protection Agency (EPA) and any State and local government requirements. (EPA's NPDW regulations can be found at 40 CFR part 141.)

Proposed § 111.15(d) would require that you use water that is of safe and sanitary quality in all aspects of your operation where, if such water was not used, could result in contamination and adulteration of your dietary ingredients and dietary supplements. Further, under proposed § 111.15(d)(2), in any operation where water contacts components, dietary ingredients, dietary supplements or any contact surfaces, the water must comply with the EPA's NPDW regulations. We believe that the EPA's NPDW water regulations are necessary because contaminated water can contaminate dietary ingredients and dietary supplements

both when used as an ingredient in the dietary ingredient or dietary supplement and when contaminated water is allowed to enter the product indirectly, as can occur, for example, when water is used to cool a product or to clean a contact surface.

We recognize that, for some operations, you may want to use water that is more pure or of higher quality than that required under the NPDW regulations. For example, to ensure the purity of your dietary supplements, you might use water that has gone through water purification and filtering equipment to ensure that the water is clean and sterile. In contrast, to clean contact surfaces and other surfaces, sterilized water may be unnecessary because a contact surface that is exposed to the environment will not remain sterile; airborne microorganisms and microorganisms on your employees will find their way onto the contact surface, thereby rendering it nonsterile. Proposed § 111.15(d) would not prevent you from using water that is more pure than that required under the NPDW regulations. Proposed § 111.15(d) provides you with the flexibility to raise your water quality above the minimum criteria to meet your particular manufacturing needs. We acknowledge that foreign firms may not be subject to EPA water requirements or adhere to EPA requirements. Nevertheless, water quality is an important part of CGMPs, so we invite comment on our proposed requirement that does not distinguish between

foreign or domestic requirements, and, therefore, would require foreign firms to meet the NPDW regulations.

A number of comments to the ANPRM suggested that we should require the use of potable water (water that is fit to drink) or a higher quality water or establish potable water as the minimum quality water standard. One comment stated that the industry outline, by referring to potable water, prevents the use of water whose quality exceeded a potable water standard because a higher quality water would not be in compliance.

We agree that potable water should be a minimum water quality standard, and proposed § 111.15(d) would reflect that standard. Proposed § 111.15(d)(1) would require water to be "safe and of adequate sanitary quality." Water that is "safe and of adequate sanitary quality" is or should be potable. Proposed § 111.15(d)(2) would require water that contacts components, dietary ingredients, dietary supplements, or contact surfaces to meet, at a minimum, EPA's NPDW regulations and State and local requirements. Water meeting these requirements is potable.

Please note that proposed § 111.15(d) does not prevent you from using water that is more pure or of higher quality than that required under EPA's NPDW regulations. We reiterate that proposed § 111.15(d) would establish minimum water quality standards.

Proposed § 111.15(d) does not make any distinctions between water from public sources and water from private sources. Consequently, if you use water from private sources, you would need to ensure that the water meets the minimum water quality standards in proposed § 111.15(d). For example, if you use a well as your water source, you would need to ensure that the well design meets government water quality standards and you may need to perform appropriate water treatment procedures, including filtration, sedimentation, and chlorination. These actions are necessary because private water sources, such as surface waters or water from shallow wells, may be subject to microbiological, chemical, or radiological contamination. For example, fertilizer runoff can enter streams and contaminate surface water. Contaminants in the ground may enter a well and contaminate well water. Therefore, it is important that water from any source comply with the requirements set out in proposed § 111.15(d).

Another comment to the ANPRM suggested that a potable water standard is inappropriate for use in manufacturing dietary ingredients and dietary supplements from chemicals. The comment would limit the use of potable water to manufacturing, processing, and handling of vegetables, ready-cooked dishes, etc.

We disagree with the comment. If water is not suitable for drinking (nonpotable), the water may contain microorganisms or contaminants that will contaminate your dietary ingredients or

dietary supplements. For example, water from private sources may be untreated, so it may be contaminated by pesticides due to water runoff from fields or may contain microorganisms, algae, particulates, etc. Therefore, proposed § 111.15(d) would require that you use water that is of safe and sanitary quality, regardless of whether you use natural or synthetic components to make dietary ingredients and dietary supplements.

Proposed § 111.15(d)(3) would require that you have documentation or otherwise be able to show that the water that contacts components, dietary ingredients, dietary supplements, or any contact surface meets the water quality standard in proposed § 111.15(d)(2). The proposal would not prescribe any particular type of documentation or method for showing water quality, but you should remember that water is used as a component in manufacturing dietary ingredients and dietary supplements would fall within the definition of "component," so it should meet whatever specifications you establish for component identity, purity, quality, strength, and composition. We discuss requirements for the identity, purity, quality, strength, and composition of components later in this section when we describe proposed § 111.35, "What production and process controls must you use?". Proposed § 111.15(d)(3) would be similar to a provision in the drug CGMP regulation at 21 CFR 211.48(a) and the proposed requirement in the infant formula proposed rule (61 FR 36154 at

36211), which requires that water meet EPA's drinking water requirements in 40 CFR part 141.

Proposed § 111.15(e) is similar to the plumbing requirements in the food CGMPs at § 110.37(b). Proposed § 111.15(e) would require your physical plant's plumbing to be adequate size and design and to be adequately installed and maintained to:

- Carry sufficient amounts of water to required locations throughout the physical plant;
- Properly convey sewage and liquid disposable waste from your physical plant;
- Avoid being a source of contamination to components, dietary ingredients, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition;
- Provide adequate floor drainage in all areas where floors are subject to flooding-cleaning or where normal operations release or discharge water or other liquid waste on the floor; and
- Not allow backflow from, or cross-connection between, piping system that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary ingredients or dietary supplements, or cleaning contact surfaces, or for use in bathrooms and hand washing facilities.

This provision is intended to ensure that your plumbing system does not adversely effect the water in your physical plant. If the plumbing system is not adequately installed and maintained, it may contaminate your water supply and, in turn, contaminate your components, dietary ingredients, and dietary supplements through direct contact, such as when you use water to make the products, or indirect contact, such as when the contaminated water is used on a contact surface.

In addition to the water directly contaminating your components, dietary ingredients, dietary supplements, or contact surfaces, standing water can cause contamination by attracting pests or becoming a breeding ground for microorganisms. Therefore, the proposal would require your plumbing system to have adequate drainage and would not allow backflows or cross-connections in your plumbing system because backflows from a nonpotable water system to a potable water system under negative pressure conditions could contaminate your water system (Ref. 57).

A comment to the ANPRM stated that requiring a physical plant's plumbing to carry sufficient amounts of water to required locations throughout the plant was too vague. The comment stated the water is not needed in many operations in the plant, and so firms should be able to decide the location and availability of water throughout their own physical plants.

The comment may have misinterpreted the ANPRM. Proposed § 111.15(d) would not require water to be available in all parts of a physical plant. In areas where water is unnecessary, we would not expect you to make water available or to have any particular quantity of volume of water available. However, there are areas where water is necessary to ensure that any unadulterated dietary ingredient or dietary supplement is manufactured, packaged or held. In those areas where water is necessary, your plumbing must carry sufficient amounts to those locations.

Proposed § 111.15(f) would require that you dispose your physical plant's sewage into an adequate sewage system or through other adequate means. This proposed provision is similar to the sewage provisions at § 110.37(c). Proper sewage disposal is essential to ensure that you maintain your manufacturing facility in a sanitary condition, and this would include protecting the processing environment against pathogenic microorganisms shed in fecal material. For example, bathroom floors can become contaminated with pathogens if your sewage disposal system fails to remove fecal material. Employees using those bathrooms, in turn, can transport those pathogens into your processing areas and contaminate components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed § 111.15(g) would apply to bathrooms. Proposed § 111.15(g) would require that you have adequate, readily accessible bathrooms for your employees and require that the bathrooms be kept clean and not become a potential source of contamination to your components, dietary ingredients, dietary supplements, or contact surfaces. The proposal would require that you keep your bathrooms from becoming potential sources of contamination. You would be required to keep the bathrooms in good repair at all times, provide self-closing doors, and provide doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination, except where you have taken other means (such as double doors or positive airflow systems) to protect against airborne contamination.

Proposed § 111.15(h) applies to hand washing facilities. The proposal would require that you provide adequate and convenient hand washing facilities that furnish running water at a suitable temperature. Proposed § 111.15(h)(1) would require that you have hand washing facilities and, where appropriate, hand sanitizing facilities at each location in your physical plant where good hygienic practices require your employees to wash or sanitize (or to both wash and sanitize) their hands.

One comment to the ANPRM suggested that, instead of requiring employees to wash "and/or" sanitize their hands, we should require employees to wash "or" sanitize their hands.

We disagree with the comments. In some cases, it is necessary to both wash and sanitize the hands. Sanitizing which generally refers to the removal or elimination of living microorganisms, may be more effective if the hands are washed before they are sanitized, and washing, alone, will not sanitize the hands. Therefore, the proposed rule would address situations where good hygienic practices require employees to wash or sanitize their hands or to wash and sanitize their hands.

Proposed § 111.15(h)(2) and (h)(3) would require that you provide effective hand-cleaning and sanitizing preparations and air driers, sanitary towel service, or other suitable drying devices. Disposable paper towels would be an example of sanitary towel service.

One comment to the ANPRM suggested replacing "effective hand-cleaning and sanitizing preparation" with "commonly available" hand-washing and sanitizing preparations.

We disagree with the comment. The purpose behind proposed § 111.15(h)(2) is to ensure that hand-cleaning and sanitizing preparations are effective. While we have objection to the use of "commonly available" hand-washing and sanitizing preparations if they are "effective," the effectiveness of the

hand-washing and sanitizing preparation is essential to ensuring that the hand-washing and sanitizing preparation will prevent adulteration of the product.

Another comment to the ANPRM suggested that a dietary supplement CGMP rule mention paper towels as a hand drying device.

We have drafted proposed § 111.15(h)(3) to identity disposable paper towels as an example of sanitary towel service. However, under proposed § 111.15(h)(3), the paper towels must be both sanitary and disposable.

Another comment to the ANPRM suggested that paper towels used in hand-washing facilities should be made from recycled paper.

We take no position regarding the use of paper towels made from recycled paper. The proposal neither requires nor prohibits the use of paper towels made from recycled paper.

Proposed § 111.15(h)(4) would require that you provide devices or fixtures that are constructed to prevent recontamination of clean, sanitized hands. For example, if sanitized hands are necessary at a particular location, you might install hand sanitizing facilities that can be activated by foot pedals or by motion so that your employees do not have to use their hands--and, by doing so, risk contaminating their hands--to turn on the hand sanitizing equipment.

Proposed § 111.15(h)(5) would require that you have easily-understood signs and to post them throughout your physical plant to direct your employees to handle components, dietary ingredients, dietary supplements, or contact surfaces to wash and, where appropriate, sanitize their hands:

- Before they start work,
- After each absence from their duty station, and
- When their hands may have become soiled or contaminated.

Proposed § 111.15(h)(6) would require that you have trash bins that are constructed and maintained in a manner to protect against recontamination of hands and contamination of components, dietary ingredients, dietary supplements, or any contact surface. The proposal would not specify any particular type of trash bin to use.

Proposed § 111.15(i) applies to trash disposal. The proposal would require that you convey, store, and dispose of trash to minimize the development of odors; to minimize the potential for trash to attract, harbor, or become a breeding place for pests; to protect against contamination of components, dietary ingredients, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant and to control hazardous waste to prevent contamination of components, dietary supplements, and contact surfaces.

Proposed § 111.15(j) would require that you assign one or more employees to supervise overall sanitation. Under the proposal, the employee or employees would have to be qualified by training and experience to develop and supervise sanitation procedures. The proposal would give you discretion in deciding how many employees you need to assign to supervise overall sanitation of your physical plant. As previously discussed, the proposed requirement does not preclude the possibility of a one-person operation. If you are a one-person operation, you would need to be qualified by training and experience to develop and perform all sanitation procedures.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for the maintenance, cleaning, and sanitation of your physical plant that describe, in sufficient detail, the maintenance, cleaning, and sanitation schedules and methods and the equipment and materials to be used. We believe that following written procedures is important because it can help you maintain your physical plant in a clean and sanitary manner. Written procedures, when used, generally have information regarding a schedule, methods, and equipment to be used to control pests. We believe that, because some insects can produce several times during their lifetime, adherence to a written procedure that provides a schedule for applying insecticides in a way that will prevent any initial and

subsequent insect infestation would be effective in preventing infestation. Such adherence would likely be a more effective way of controlling pests than attempting to apply insecticides only after you have noticed insects in your physical plant. As another example, written procedures for cleaning your physical plant may specify the use of a particular cleaning compound in a specific strength or concentration; if you do not establish and follow those written procedures, you may use the wrong cleaning compound, use a cleaning compound too strong and create odors that may contaminate or affect your components, dietary ingredients, or dietary supplements, or use a cleaning compound that is too weak and, therefore, ineffective. As stated previously, we invite comment on whether written procedures for maintenance, cleaning, and sanitation should be required in a final rule, and whether there are other written procedures, in addition to those mentioned, that we should include in a final rule.

As stated previously, we invite comment on whether documentation at the time of performance of equipment, utensil, and contact surface maintenance, cleaning, and sanitation and keeping such records should be required in a final rule. However, the proposal would require that the batch production record must show the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in

producing the batch. This would give you a record that you would be able to consult if any questions regarding maintenance, cleaning, and sanitation of equipment used in producing the batch arise.

2. What Design and Construction Requirements Apply to Your Physical Plant? (Proposed § 111.20)

Proposed § 111.20 would describe the general requirements for physical plant construction and design that are necessary to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding.

Proposed § 111.20(a) would require any physical plant you use in the manufacturing, packaging, or holding of dietary ingredients or dietary supplements to be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations. You should note that proposed § 111.20(a) refers to cleaning operations and to sanitizing operations. Although these terms appear to be similar, they are distinct in the sense that a sanitizing operation usually produces a sterile (free of living microorganisms) environment whereas a cleaning operation may not. To illustrate the difference, if you wipe a contact surface with a wet cloth to remove any components or dietary ingredients, you would have engaged in a cleaning operation. The contact surface is free of noticeable debris, but it might still contain microorganisms. In contrast, if you used

a disinfectant on the contact surface in order to eliminate any possible microorganisms on that surface, you would have engaged in a sanitizing operation.

Size, construction, and design of a physical plant are important to manufacturing, packaging, and holding dietary ingredients and dietary supplements that are not adulterated because they can help you identify and eliminate possible sources of contamination that result in or may lead to adulteration. For example, condensation can occur on water pipes. If these pipes are exposed and run above a contact surface, condensation from those pipes may fall onto the contact surface and adulterate your dietary ingredients or dietary supplements. So, if you design your physical plant to eliminate exposed pipes or to shield your contact surfaces from condensation, you would eliminate a possible source of adulteration.

As another example, you might find it more practical to clean certain floors in your physical plant by spraying them with water. Obviously, a floor design that uses floor drains would facilitate the cleaning of those floors.

Proposed § 111.20(b) would require your physical plant to 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, dietary ingredients, and dietary supplements

during manufacturing, packaging, or holding. Adequate space for the orderly placement of equipment and holding of materials is important because it can directly affect your ability to maintain, clean, or sanitize your equipment or physical plant effectively. For example, assume that your manufacturing operation involves the use of a large mixer. However, the mixer is installed in a small room which makes it difficult to open the mixer fully. This may make it difficult for you to maintain and clean the mixer properly and, as a result, may increase the possibility that residues in the mixer will contaminate the next batch of ingredients that go into the mixer.

Proposed § 111.20(c) would require your physical plant to permit the use of proper precautions to reduce the potential for mixups or contamination of components, dietary ingredients, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material. The proposal would require the physical plant to have, and require that you 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, dietary ingredients, and dietary supplements during specific operations. The specific operations would be listed at proposed § 111.20(c)(1) through (c)(7) and are as follows:

- Receiving, identifying, holding, and withholding from use, components, dietary ingredients, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, or holding of dietary ingredients and dietary supplements;
- Separating, as necessary, components, dietary ingredients, dietary supplements, packaging, and labels that are to be used from components, dietary ingredients, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection;
- Separating the manufacturing, packaging, and holding of different product types, including, but not limited to, different types of dietary ingredients, dietary supplements, and other foods, cosmetics, and pharmaceutical products;
- Performing laboratory analyses and holding laboratory supplies and samples;
- Cleaning and sanitizing contact surfaces;
- Packaging and label operations; and
- Holding dietary ingredients or dietary supplements.

The proposal would not specify the types of precautions your physical plant must have to reduce the potential for mixups or

contamination. The precautions may depend on your physical plant and the products you make. For example, depending on your physical plant's size and layout, you may be able to receive components and dietary ingredients at one location, hold them in another location and store rejected components and dietary ingredients in yet another location. However, if your physical plant does not allow for physically separate areas, you would have to develop an alternative approach for segregating components, dietary ingredients, and dietary supplements at points when they are received, stored, and rejected.

Proposed § 111.20(d) would require that your physical plant be designed and constructed in a manner that prevents contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The proposal would require that the design and construction include floors, walls, and ceilings that are of smooth and hard surfaces that may be adequately cleaned and kept clean and in good repair. Smooth, hard surfaces are necessary because they are easier to clean and sanitize than those surfaces that are not smooth and hard. The proposal also would require that you use fixtures, ducts, and pipes that do not contaminate components, dietary ingredients, dietary supplements, or contact surfaces by dripping or condensate. Condensation may contain microorganisms or

contaminants that can contaminate your components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed § 111.20(d) also would require your physical plant's design and construction to:

- Use 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 ingredients, dietary supplements or contact surfaces. Adequate ventilation or environmental control equipment is a necessary part of your physical plant's design and construction because some contaminants and microorganisms may be airborne, so a failure to provide adequate ventilation will increase your chances of airborne contamination. In addition, some potentially harmful gases (such as carbon monoxide and carbon dioxide) are colorless and odorless, so it is important to have a ventilation or environmental control system that minimizes odors and vapors;
- Use fans and other air-blowing 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;

- Use equipment to control temperature and humidity. For example, high temperatures may stimulate reproduction of microorganisms and pests, and these microorganisms and pests may, in turn, contaminate your components, dietary ingredients, dietary supplements, and contact surfaces; and
- Include 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 ingredients, dietary supplements, or contact surfaces with clothing or personal contact. For example, your employees will perform their duties more efficiently and more effectively if they have sufficient space to perform those duties. The clothing worn by your employees will be less likely to be a source of contamination if there is sufficient space between your employees and your components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed § 111.20(e) would require your physical plant to provide adequate light in all areas where components, dietary ingredients, or dietary supplements are examined, processed, or

held and in all areas where contact surfaces are cleaned. Proposed § 111.20(e) also would require that you provide adequate lighting in hand washing areas, dressing and locker rooms, and bathrooms. Inadequate lighting in areas where components, dietary ingredients, or dietary supplements are examined, processed, or held may make it difficult to examine a component or read a label; as a result, incorrect ingredients may be used in a dietary supplement. Adequate lighting also is important in areas where contact surfaces are cleaned to ensure that the contact surfaces have been cleaned properly. Adequate lighting is important in hand-washing areas, dressing and locker rooms to ensure that personal cleanliness is maintained in accordance with proposed § 111.10(b).

Proposed § 111.20(f) would require your physical plant to use safety-type light bulbs, fixtures, skylights, or other glass that is suspended over exposed components, dietary ingredients, or dietary supplements in any step of preparation, unless otherwise constructed in a manner that will protect against contamination in case of glass breakage. These precautions are necessary because glass shards can be very small and difficult to see, and some lights may spread their contents if they burst or explode. So, to protect your components, dietary ingredients, and dietary supplements, the proposal would require your physical

plant to take precautions concerning your lighting and other suspended glass.

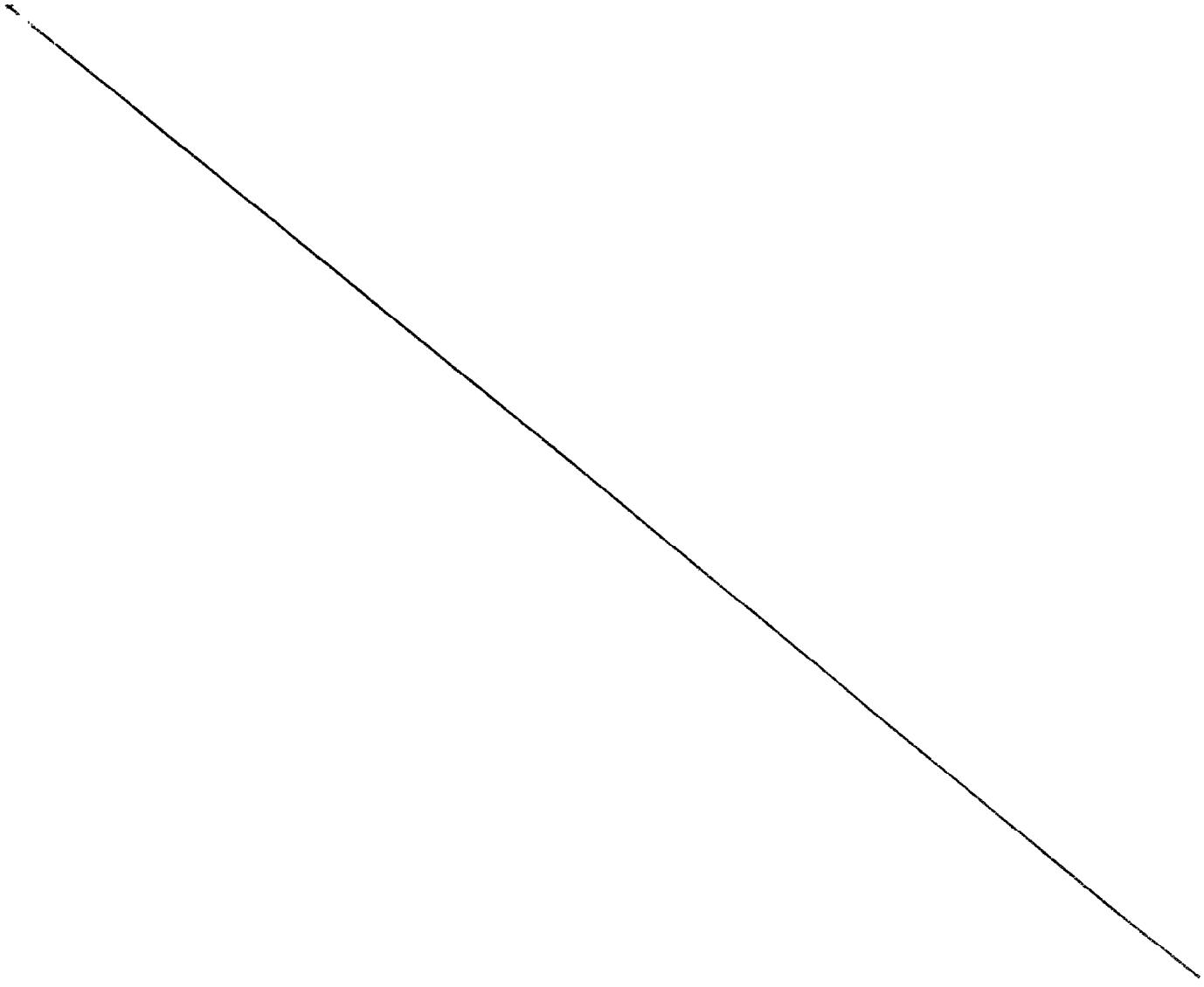
Proposed § 111.20(g) would require that your physical plant provide protection by any effective means against contamination of components, dietary ingredients, and dietary supplements in bulk fermentation vessels. The proposal describes some means to consider, such as using protective coverings, placement in areas where you can eliminate harborages for pests over and around vessels, placing bulk fermentation vessels in areas where you can check regularly for pests, pest infestation, filth, or other extraneous material, and using skimming equipment. You must protect components, dietary ingredients, and dietary supplements held in bulk fermentation vessels because, if the contents of a bulk fermentation vessel are contaminated, those contaminated contents may be used to make many dietary ingredients or dietary supplements that, as a result, would be adulterated.

Proposed § 111.20(h) would require your physical plant to include adequate screening or other protection against pests, where necessary. This provision would be one measure to exclude certain pests from the physical plant that also may assist you in complying with proposed § 111.15(c). As we explained earlier in the discussion of proposed § 111.15(c), pests are a potential source of contamination because they may carry microorganisms,

shed hair or feathers, leave droppings, or carry filth or dirt into your physical plant.

D. Equipment and Utensils (Proposed Subpart D)

Proposed subpart D consists of two provisions. These proposed provisions consist of general requirements for equipment and utensils and for automatic equipment, including computerized systems, hardware, and software.



1. What Requirements Apply to the Equipment and Utensils You Use? (Proposed § 111.25)

Proposed § 111.25 would establish general requirements pertaining to equipment design, construction, and sanitation. For example, proposed § 111.25(a)(1) would require that you use equipment and utensils of appropriate design, construction, and workmanship that would enable them to be suitable for their intended use, adequately cleaned, and properly maintained. The equipment and utensils covered under the proposal would include, but not be limited to:

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

To show how proposed § 111.25(a)(1) might apply, assume that you use a mixer to blend powdered ingredients. If the mixer blade is too small, it might not mix the ingredients properly or thoroughly, and the resulting batches might be adulterated if the ingredients are not provided at the required levels throughout the batch. In this example, the mixer was not suited for its intended use. As another example, if your manufacturing

equipment is so complex or designed in a way that makes cleaning difficult, any unclean surfaces on that equipment could become a source of contamination in the future. In this case, the equipment was not adequately cleaned and properly maintained or, alternatively, was not of appropriate design for its intended uses.

Proposed § 111.25(a)(2) would require that you use equipment and utensils of appropriate design and construction whose use will not result in the contamination of your components, dietary ingredients, or dietary supplements with lubricants, fuel, coolants, metal or glass fragments, filth or other extraneous material, contaminated water, or any other contaminants.

Proposed § 111.25(a)(3) would require your equipment and utensils to be:

- Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;
- Corrosion-resistant if the equipment or utensils contact components, dietary ingredients, or dietary supplements;
- Made of nontoxic materials;
- Designed and constructed to withstand the environment of their intended use, the action of components, dietary ingredients, or dietary supplements, and, if

applicable, cleaning compounds and sanitizing agents; and

- Maintained to protect components, dietary ingredients, and dietary supplements from being contaminated by any source.

Deteriorating equipment can be a source of contamination. For example, repeated contact between metal surfaces in a grinding or tableting machine can result in metal fragments that can contaminate your dietary ingredients or dietary supplements. So, your equipment and utensils must be designed and constructed to withstand the environment of their intended use and you must maintain your equipment and utensils to guard against contamination.

Proposed § 111.25(a)(4) would require your equipment and utensils to have seams that are smoothly bonded or maintained to minimize accumulation of component, dietary ingredient, or dietary supplement particles, dirt, filth, organic material, or any other extraneous material or contaminants. We are proposing this requirement because equipment and utensils containing breaks, pits, cuts, or grooves can be difficult to clean, and the pores or crevices in those breaks, pits, cuts, or grooves can become a breeding ground for microorganisms and insulate them from cleaning and sanitizing agents.

Proposed § 111.25(a)(5) would require freezers and cold storage compartments that hold components, dietary ingredients, or dietary supplements to be fitted with accurate thermometers or other temperature-measuring or temperature-recording devices and would recommend automatic devices for regulating temperature or for sounding an alarm to indicate significant temperature changes in a manual operation. These devices are necessary to ensure that you are able to monitor the temperatures where you hold your components, dietary ingredients, or dietary supplements and to indicate whether they were held at appropriate temperatures to minimize the growth of pathogens and to prevent deterioration.

While we patterned proposed § 111.25(a)(5) after a provision in the food CGMPs (§ 110.40(e)), we invite comment on whether we should require specific target temperatures for dietary ingredients or dietary supplements held in freezers or cold storage, and if so, what those temperatures should be and why.

Proposed § 111.25(a)(6) would require instruments or controls used in the manufacturing, packaging, or holding of a dietary ingredient or dietary supplement to be accurate and precise, adequately maintained, and adequate in number for their designated uses. By using the words, "accurate and precise," we mean that the instruments or controls must be accurate--the recorded measurements are equal to the true value of the thing being measured--and precise--individual measurements should be

close to each other when made under the same conditions. For example, if the temperature inside a particular piece of equipment is 100 °F, and your thermometer for that piece of equipment reads a temperature of 100 °F, the thermometer is accurate. If multiple temperature readings for that thermometer ranged from 99.7 °F to 100.4 °F, and the variation in temperature was not significant statistically, you could say the thermometer is precise. The proposed requirement identifies examples of such instruments and controls, such as instruments or controls you use to measure, regulate, or record:

- Temperatures;
- pH;
- Water activity; or
- Other conditions that control or prevent the growth of microorganisms or other contamination.

Instruments or controls that affect the environment, such as instruments that regulate temperature, pH, and water activity, are important because environmental factors can influence microorganism growth and deterioration. For example, changes in water activity (a_w) can have a dramatic impact on microorganism growth. A population of Salmonella typhimurium is reduced tenfold in 0.18 minutes at 60 °C if the a_w for the suspending medium is 0.995. If the a_w is 0.94, it takes 4.3 minutes (or

nearly 24 times as long) at 60 °C to achieve the same tenfold reduction (Ref. 58).

Adequate maintenance is an important part of proposed § 111.25(a)(6). If you fail to properly maintain your instruments and controls, they may produce unreliable readings and contribute towards the contamination and adulteration of your dietary ingredients and dietary supplements. For example, assume that you refrigerate a particular dietary ingredient to prevent microorganism growth. If your refrigerator gives you the wrong temperature readings so that the actual temperature inside your refrigerator is too high, you may be unaware of microorganism growth that has occurred on your dietary ingredient. Similarly, if the actual temperature inside your refrigerator is too low so that you unintentionally froze the dietary ingredient, the freezing process may have produced a chemical change in your dietary ingredient that will cause it to be out of specification.

Note, too, that the proposal also would require that your instruments and controls be adequate in number for their designated uses. For example, if the temperature of a large piece of equipment needs to be monitored, several temperature-indicating devices may be needed to accurately monitor the temperature in all parts of the equipment.

A comment to the ANPRM objected to requiring all instruments and controls used in all aspects of dietary supplement

manufacturing be accurate. The comment said such a requirement would imply strongly a need for validation, but that validation is a standard applicable to drug CGMPs, but not to food CGMPs. The comment said that a dietary supplement CGMP rule should not require validation of instruments and controls.

We disagree with the comment's objection to requiring all instrument and controls be accurate because, as we stated earlier, inaccurate instruments and controls may generate inaccurate readings, and those readings may adulterate your dietary ingredients and dietary supplements. We believe that all instruments and controls used in the manufacture, packaging, and holding of dietary ingredients and dietary supplements be accurate and precise, adequately maintained, and adequate in number for their designated uses.

We further disagree that the principles of validation are applicable to drugs, but not to foods. We stated in a previous FDA publication (Ref. 59) that the "computerized system used to control critical functions in food processing should be validated in its entirety." We have no basis to conclude that validation of instruments and controls is a standard applicable to drugs and not to foods, nor did the comment provide a reason for its assertion that validation does not apply to foods. We invite comment in this proposal on whether we should include requirements in a final rule, that would address the same or

similar concerns that the principles of validation would address. We also invite comment on whether there are other procedures that we should include in a final rule.

Proposed § 111.25(a)(7) would require compressed air and other gases that are introduced into or onto a component, dietary ingredient, dietary supplement, or contact surface or that are used to clean contact surfaces to be treated in a way so that they do not contaminate the component, dietary ingredient, dietary supplement or contact surface. Air or other gases that are not properly treated and filtered, or air that is not of the proper purity, can introduce contaminants into the dietary supplement product and adulterate it. Also, compressed gases can be contaminated with oil from the equipment (such as an air compressor) or with filth or microbiological contaminants from the compression, storage, or distribution equipment. So, if left untreated, the compressed air can deposit those contaminants onto your components, dietary ingredients, dietary supplements, and contact surfaces. Filtration at the air intake and after compression, storage, and distribution may be an effective means of reducing the risk that such contaminants will enter the compressed air or other gases.

Proposed § 111.25(b)(1) would require that you calibrate your instruments and controls that you use in manufacturing or testing components, dietary ingredients, or dietary supplements.

Proposed § 111.25(b)(2) would require that you calibrate before you first use the instruments and controls and either as specified in writing by the manufacturer of the instrument and control or at routine intervals or as otherwise necessary to ensure their accuracy and precision. Calibrating instruments and controls will ensure that they are accurate and precise and that the instrument or control readings are "true values." We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for calibrating instruments and controls, and whether there are other procedures, that we should consider including in a final rule.

Proposed § 111.25(c) would require the person who performs the instrument or control calibration to document, at the time of performance, that he or she performed the calibration. The proposal would require this documentation to include, but not be limited to:

- The instrument or control calibrated;
- The date of calibration;
- The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy. A certification of accuracy usually accompanies a standard reference material and often is valid for a specific period of time, but the supplier of the

reference standard may recertify the standard's accuracy. The recertification typically involves testing by the supplier to verify that the material maintains accuracy as a testing reference. This information also may help you trace the source of a problem, if one arises, in your dietary ingredients or dietary supplements. For example, if consumers report an adverse event with a batch of dietary supplements, records containing a certification of accuracy of the reference standards used and a history of their recertification would help you determine if the problem resulted from using an inaccurate reference standard to calibrate your instruments;

- The calibration method used including appropriate limits for accuracy and precision of instruments and controls when calibrating;
- The calibration reading or readings found;
- The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and
- The initials of the person who performed the calibration.

These records will enable you to determine whether the calibration schedule can maintain the accuracy of your

instruments and controls, and will also provide information on when and how the instruments and controls were calibrated in case a problem arises with a batch of dietary ingredients or dietary supplements. If you examine these records over time, you also will be able to see how precise your instruments and controls are and to make any necessary adjustments or repairs. For example, if your records show that a scale gives a particular reading for a standard reference weight in January, but then shows a different reading in June for the same standard reference weight, you may need to adjust, repair, or even replace your scale.

In fact, proposed § 111.25(d) would require that you repair or replace instruments and controls that cannot be adjusted to agree with the reference standard. You should not trust any instrument or control that cannot be adjusted to agree with a reference standard because an inaccurate measurement or reading may result in an adulterated dietary ingredient or dietary supplement. Again, to use a scale as an example, if you have a scale that you cannot adjust to read the correct weight, using that scale to weigh a dietary ingredient to be added to a particular mix would cause you to add either too much or too little of the dietary ingredient into your mix, thus throwing your mix out of specification. So, proposed § 111.25(d) would require that you repair or replace that scale.

Proposed § 111.25(e) applies to maintenance and sanitation. The word "maintenance," in this provision, means the act of keeping your equipment and utensils in working order as recommended by their manufacturer. Proposed § 111.25(e)(1) would require that you maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements and to take apart your equipment and utensils as necessary for thorough maintenance, cleaning, and sanitizing. Obviously, if you fail to keep your equipment, utensils, and contact surfaces clean, you risk contaminating them with microorganisms and other contaminants and risk transferring those microorganisms or other contaminants to anything that touches the equipment, utensils, and contact surfaces.

Proposed § 111.25(e)(2) would require that you ensure that all contact surfaces used for manufacturing or holding low-moisture components, dietary ingredients, or dietary supplements are in a dry and sanitary condition at the time of their use. If the surfaces are wet-cleaned, you must sanitize them, when necessary, and allow them to dry thoroughly before you use them again.

Thoroughly drying equipment before it is used for manufacturing or holding dry dietary products is essential to ensure that the equipment will not change the composition of the

dry product. For example, if moisture is left on equipment, the moisture will become a part of the product and may change the composition of the product. Moist surfaces can also promote microorganism growth, and microorganisms can adulterate your components, dietary ingredients, or dietary supplements.

Proposed § 111.25(e)(3) would apply if you use wet processing during manufacturing. Under the proposal, you would have to clean and sanitize all contact surfaces as necessary to protect against the introduction of microorganisms into components, dietary ingredients, or dietary supplements. Proposed § 111.25(e)(3) also would require that, when cleaning and sanitizing is necessary, you must clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may become contaminated. If you use contact surfaces in a continuous production operation or in back-to-back operations involving different batches of the same dietary ingredient or dietary supplement, the proposal would require that you clean and sanitize the contact surfaces as necessary.

Proposed § 111.25(e)(4) would complement proposed § 111.25(e)(2) and (e)(3) by requiring that you clean, as frequently as necessary, surfaces that do not touch components, dietary ingredients, or dietary supplements to protect against contamination. 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, dietary ingredients, 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 ingredients, dietary supplements, and contact surfaces.

Proposed § 111.25(e)(5) would establish requirements for single-service articles, such as utensils intended for one-time use, paper cups, and paper towels. Proposed § 111.25(e)(5) would require these articles to be stored in appropriate containers and handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface. For example, you would not place a paper towel dispenser over a contact surface because persons reaching for those paper towels might drip contaminated water or other fluids onto the contact surface. Inadvertent reuse of a single-service article also could lead to contamination, so disposing of single-service articles is an important element in proposed § 111.25(e)(5).

Proposed § 111.25(e)(6) would require your cleaning compounds and sanitizing agents to be adequate for their intended uses and safe under their conditions of use. An adequate cleaning compound is one that will lower the surface tension of water so that spills can be lifted and flushed away (Ref. 60).

Ordinary soap has a limited ability to solubilize fats, oils, and proteins. Inorganic alkaline detergents can dissolve food solids, such as fats and proteins, but mineral deposits will frequently require the use of acid cleaners (Ref. 60). Proposed § 111.25(e)(6) would not prescribe any particular cleaning compound. Instead, you may select cleaning compounds that are suited to your particular needs. An adequate sanitizing agent is one that has a bactericidal effect on the types of microorganisms normally present in the physical plant environment and is safe, chemically stable, and convenient for use. However, sanitizing agents can achieve their intended effect only after they are applied to a surface that has been thoroughly cleaned, and if they are applied at a proper concentration (Ref. 61).

Proposed § 111.25(e)(7) would require that you store cleaned and sanitized portable equipment and utensils that have a contact surface in locations and in a manner that protect them from contamination. This requirement is necessary to ensure that your portable equipment remains clean and sanitized until used; otherwise, if the contact surfaces on the portable equipment or utensils become contaminated, they could lead to adulteration of your dietary ingredients or dietary supplements.

We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for maintenance, cleaning, and sanitizing. Further, we invite

comment on whether we should require that the person who performs the maintenance, cleaning, and sanitizing described in this section document, at the time of performance that the maintenance, cleaning, and sanitizing were performed. The documentation of maintenance, cleaning, and sanitizing performance, if we were to require this in a final rule, could contain requirements for showing:

- Specific equipment to be maintained, cleaned, or sanitized;
- The maintenance, cleaning, and sanitation methods used;
- The initials or name of the individual who performs the maintenance, cleaning, or sanitizing;
- The initials or name of the supervisor who verifies that the maintenance, cleaning, and sanitizing procedures were performed; and
- The date and time of each maintenance, cleaning, and sanitizing.

These procedures may help ensure that certain steps were taken to maintain, clean, and sanitize equipment, show how and when they were done, and show who performed and who supervised those steps. Those procedures may be helpful to inform you that equipment is being maintained, cleaned, and sanitized regularly and as frequently as is necessary based on the actual use, as opposed to the planned use, of the equipment. For example, you

may need to clean your equipment more frequently if the actual rate of production using that equipment consistently exceeds the predicted rate of production. As stated earlier, we invite comment on whether written procedures for maintenance, cleaning, and sanitizing equipment, utensils, and contact surfaces and records documenting that the procedures were followed should be included in a final rule, and whether there are procedures, other than those mentioned, that we should include in a final rule.

As discussed later, proposed § 111.50(c)(4) would require that you document, in the batch production record, the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used to producing the batch. Records that document the batch or lot number of each batch or lot of dietary ingredients or dietary supplements processed using a particular piece of equipment or a particular utensil between equipment startup and shutdown for maintenance, cleaning, and sanitizing will allow you to identify all dietary ingredients or dietary supplements that may have been manufactured or packaged with a specific piece of equipment or utensil if you later discover that the equipment or utensil was improperly maintained, cleaned, or sanitized.

Proposed § 111.25(f) would require that you keep calibration records as required by this section in accordance with the recordkeeping requirements in proposed § 111.125. Such records

will verify for you and the agency that calibrations are performed. More importantly, these records will help you ensure that all calibrations are performed. If problems do occur with the production of a product, these records will help you determine whether those problems are associated with faulty calibrations. These records will help you determine which batches were produced under these conditions. Further, these records will help you train employees or adjust the calibration schedule as needed to avoid further problems.

2. What Requirements Apply to Automatic, Mechanical, or Electronic Equipment? (Proposed § 111.30)

Manufacturers of dietary ingredients and dietary supplements often rely on automatic, mechanical, and electronic equipment in production. Automated equipment is often used to ensure proper formulation, mixing, and processing or to test a batch of dietary ingredient or dietary supplement. Such automated equipment frequently consists of a computer or system of computers that control many or all stages of production, inprocess sampling, and testing. It is important that such systems and equipment function as expected to ensure that the dietary ingredient or dietary supplement contains the correct ingredients in the appropriate amounts and is manufactured according to these CGMP proposed requirements, and thus, is not adulterated under section 402(g) of the act.

Proposed § 111.30 sets forth requirements for automatic, mechanical, or electronic equipment. These types of equipment include, for example, mechanical equipment such as a scale used to weigh bulk components and electronic equipment such as a computerized blending machine.

Proposed § 111.30(a) would allow you to use automatic, mechanical or electronic equipment to manufacture, package, label, and hold a dietary ingredient or dietary supplement. Thus, the proposal would let you decide what type of equipment meets your needs. Proposed § 111.30(a)(1) would require that you must design or select equipment to ensure that dietary ingredient or dietary supplement specifications are consistently achieved. Equipment used in dietary ingredient or dietary supplement manufacturing, packaging, and label operations must be, for example, of an appropriate size and installed properly in order to produce an unadulterated product. If not designed or installed properly, the equipment can lead to a variety of problems. For example, a mixer for the blending of powdered ingredients will not properly perform its function if the blade is too small relative to the size of the mixer or not properly placed inside of the mixer. Such a mixer may produce an adulterated product because the dietary supplement, for example, is not of uniform composition and therefore would not be able to meet the specifications for purity, quality, strength, or

composition in the final product. Thus, equipment design and selection is critical to ensure that you manufacture an unadulterated dietary ingredient or dietary supplement.

Proposed § 111.30(a)(2) would require that you determine the suitability of your equipment. The equipment that you use must be capable of operating satisfactorily within the operating limits required by the process. The equipment must function as intended. 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 the system, tested under conditions that reflect actual conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime.

Moreover, the incorporation of software into the operation of automatic equipment has not only increased the complexity of such equipment but also has 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, proposed § 111.30(a) would require

that you exercise appropriate controls over systems and, in particular, over the software used in the systems.

Proposed § 111.30(b) would require, for any automatic, mechanical, or electronic equipment that you use, that you must:

- Routinely calibrate, inspect, or check to ensure proper performance.
- Make and keep written records of equipment calibrations, inspections, or checks;
- Establish and use appropriate controls to ensure that your quality control unit approves changes in master manufacturing record, batch control records, packaging operations and label operations, or changes related to the equipment that you use and that only authorized personnel institute the changes;
- Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use and have your quality control unit approve these controls; and
- Make and keep backup file(s) of software programs and of data entered into your computer system. Your backup file may be a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks but must be an exact and complete record of the data you entered. We also propose to require that you keep your

backup software programs and data secure from alterations, inadvertent erasures, or loss. In this way, you have a record of changes to your software program and of your current software program used in manufacturing. This information is important to both identify any production errors or discrepancies and to make necessary corrections. Such records will allow you to troubleshoot and to operate these systems with a minimum of interruption when problems occur because the records will include a copy of all software used and a backup file of data entered into the computer or related system which can be used to reload the system. The records also will provide information that you can use in trying to determine why a problem with the system is occurring or why the system is not producing a dietary ingredient or dietary supplement that complies with your specifications for the product.

Appropriate controls that you establish and use for automated measuring, regulating, or recording temperatures, pH, acidity, water activity, or other conditions will minimize the potential for growth of microorganisms, for contamination, or for adding too much or too little of a dietary ingredient. Observations, inspections, and checks of the equipment will help you to determine if critical factors such as revolutions per

minute, temperatures, pressures, process times, and automatic documentation are being controlled by the system. Under proposed § 111.30(b), examples of controls to ensure that the equipment functions in accordance with its intended use include:

- Determining the extent and frequency of calibration, inspections and checks to ensure proper performance;
- Determining and using predetermined action plans when an alarm sounds indicating an out-of-limits situation or malfunction;
- Checking in-put and out-put on a sufficient basis to provide a high degree of assurance that input and output is accurate;
- Comparing manual calculations of data with the automated calculations on a sufficient basis to provide a high degree of assurance that the automated calculations are accurate; and
- Determining the adequacy of automated cleaning and residue elimination.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for the calibration, inspection, and checking of automatic equipment to ensure that procedures are performed consistently and in an appropriate way. In addition, we invite comment on whether there

are procedures, other than those mentioned, that we should include in a final rule.

For computerized equipment, you should note that we already have issued guidance documents that may give you some helpful information. The guidance documents are: "FDA Guide to Inspections of Computerized Systems in the Food Processing Industry" (Ref. 59), and a "Guide to Inspections of Computerized Systems in Drug Processing" (Ref. 62). Although we did not draft these guidance documents for dietary ingredient and dietary supplement firms, they still provide important advice on establishing and using computerized systems in dietary supplement manufacturing operations. Given the broad range in sophistication, complexity, and computerization in manufacturing equipment, we invite comments on whether we should regulate computerized systems separately from other automatic equipment.

Although we are not proposing verification requirements in this proposed rule, we are seeking comment on whether such verification should be included in a final rule. Verification would ensure that the processes using automatic, mechanical, and electronic equipment consistently produce an outcome that meets a predetermined specification and any predetermined quality characteristics. Verification is important because it shows you whether your automatic, mechanical, or electronic processes will consistently operate as they should.

We believe, in general, that scientific knowledge and industry experience have defined the basic elements of a sound verification system. Those elements include:

- Determining whether the capacity of the hardware matches its assigned function. For example, in a system using a resistance temperature device (RTD) for temperature control, is the RTD capable of sensing temperatures throughout the processing control range, has the RTD been checked for accuracy in the operating temperature range(s), does the computer receive an accurate signal from the RTD, and does the computer react to the RTD signals as designed?
- Identifying and considering operational limits in establishing production procedures. For example, a programmable logic controller (PLC) may be able to only receive input from two thermocouples at one time. This would limit the number of locations at which temperatures could be obtained in this manufacturing process.
- Determining whether the software matches the assigned operational function. For example, if software is assigned to generate complete processing records, does it include all the information required to be recorded?

- Testing simulated production conditions including "worst case" conditions. Equipment may function well under minimal production stress but falter under high stresses of equipment speed, data input overload or frequent or continuous multi-shift use, unexpected sequences or order of events and a harsh environment.
- Repeating tests enough times to assure a reasonable measure of consistent reproducible results. In general, at least three consecutive, successful test runs should be made to cover different operating conditions.
- Documenting the verification program. Documentation should include a verification protocol and test results that are specific and meaningful in relation to the attribute being tested. For example, if a temperature sensor's reliability is being tested, it would be insufficient to express the results merely as "acceptable," without other qualifying data such as temperatures observed, duration of the test, and the temperature range tested. The individual(s) responsible for conducting, reviewing, and approval of the verification should be identified in the documentation.

- Initiating reverification when significant changes are made to the system or when errors are noted. For example, reverification is needed when a major piece of equipment is replaced and when software changes such as time, temperature, sequence of routine events, data edits, or data handling are made.

These verification elements differ from the controls that ensure equipment functions in accordance with its intended use as described in proposed § 111.30(b). The controls established under proposed § 111.30(b) would routinely monitor certain equipment operations. Equipment and process verification is primarily performed before first use to support a high degree of confidence that the equipment will consistently perform as it is supposed to and when significant changes are made or when system errors are noted. FDA believes it is important to verify that equipment performs as it should before first use and thereafter as needed. For example, when certain changes are made to the system, verification is necessary for protecting the integrity of the dietary ingredient and dietary supplement manufacturing process. Although your verification steps will vary according to the nature of the dietary supplement and the complexity of the process, the basic elements of a verification system would be generally applicable to all dietary ingredients and dietary supplements and provide a foundation for building a comprehensive

approach to ensure that the equipment performs in a predetermined way. Verification is relevant to all equipment processes, including but not limited to computerized systems involved in the manufacturing process. (In this instance, the term "verification processes" includes initial verification and reverification.) Verification applies to all manufacturing steps in the creation of the finished product, including but not limited to cleaning, weighing, measuring, mixing, blending, compressing, filling, packaging, and labeling.

As stated earlier, we invite comment on whether automatic, mechanical, and electronic equipment verification and reverification elements that we have discussed should be done, should be included in the final rule as requirements, which would include requirements to document the verification steps. Additionally, we seek comment if other verification steps not discussed here should be included and we intend to consider such comments in a final rule. Finally, given the broad range in sophistication, complexity, and computerization in manufacturing equipment, we invite comment on whether we should regulate computerized systems separately from other automatic equipment.

E. Production and Process Controls (Proposed Subpart E)

Proposed subpart E contains production and process controls to help ensure that you have controls covering all manufacturing, packaging, label, and holding operations, and that those controls

will prevent adulteration of your dietary ingredient or dietary supplement. We propose to establish a framework in which decisions about producing a dietary ingredient or dietary supplement are left to you, but that charges you with incorporating into your production process, measures that are designed to ensure that the dietary ingredient or dietary supplement is manufactured in a manner that will prevent adulteration and misbranding.

Dietary ingredient and dietary supplement manufacturing requires technical knowledge and skill (e.g., in research and development, production equipment and procedures, and analytical equipment and methodology) that a vast majority of companies in the food processing industry do not have. A dietary ingredient or dietary supplement manufacturer must maintain constant control because a seemingly innocuous change in the formulation or preparation method or in exposure to an unanticipated environmental condition could create a health hazard. Earlier, in section I.E of this document in our discussion of "FDA's Decision to Propose a Rule," we cite several examples of problems arising from poorly controlled manufacturing practices. For example, we cite problems of dietary ingredient misidentification; super- and subpotent dietary supplements; and contamination including toxic substances, microorganisms of public health significance, and heavy metals. Thus, we believe

that using a production and inprocess control system covering all stages of processing is necessary to insure that the dietary ingredient or dietary supplement is manufactured in a manner that will prevent adulteration.

1. What Production and Process Controls Must You Use? (Proposed § 111.35)

Proposed § 111.35(a) would require that you implement a system of production and inprocess controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary ingredients and dietary supplements.

Proposed § 111.35(b) would require that your production and inprocess control system must be designed to ensure that you manufacture, package, or hold dietary ingredients or dietary supplements in a manner that will prevent their adulteration. The proposal would require that your production and inprocess control system must include all requirements of this subpart and also would require your quality control unit to review and approve the production and inprocess control system. We believe that requiring a production and inprocess control system is necessary to provide consistency in producing different batches of dietary ingredients or dietary supplements and to facilitate preparing each batch.

Proposed § 111.35(c) would require that you use your quality control unit in your manufacturing, packaging, and label

operations to ensure that these operations are performed in a manner that prevents adulteration and to ensure that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

Proposed § 111.35(d) establishes requirements for any substance that may be used in a dietary ingredient or a dietary supplement. This section would require that any substance that is used be a "dietary ingredient" within the meaning of that term in section 201(ff) of the act, or, if not included with the meaning of that term, must meet the applicable statutory and regulatory requirements under section 409 of the act, or section 721 of the act (21 U.S.C 379e) if a color additive, to ensure that the substance is safe and lawful for use in a dietary ingredient or a dietary supplement.

A "dietary ingredient" within the meaning of section 201(ff) of the act that is in, or intended for use in, a dietary supplement is exempt from the definition of "food additive" in section 201(s). Such "dietary ingredients" are not subject to the premarket approval standard for food additives under section 409 of the act. However, under section 402(f)(1) of the act, in order for a dietary ingredient or a dietary supplement not to be deemed adulterated, substances that are "dietary ingredients" that are used in the manufacture of a dietary ingredient or a dietary supplement must not present a significant

or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or, if no such labeling, under ordinary conditions of use. In addition, there must be adequate information to provide reasonable assurance that a new dietary ingredient does not present a significant or unreasonable risk of illness or injury. Further, under section 402(f)(1) of the act, dietary ingredients must not be poisonous or deleterious substances within the meaning of section 402(a)(1) of the act. Thus, manufacturers have a responsibility to ensure that the dietary ingredients and dietary supplements that they produce are not adulterated under section 402(f) of the act.

However, certain substances are not "dietary ingredients" within the meaning of section 201(ff) of the act, and thus, are not exempt under section 201(s) from regulation as a food additive under section 409 of the act. Such substances include components that are added to provide certain technical effects to the dietary supplement, such as disintegration, lubrication, or binding. In addition, such substances may include color additives that are used or intended for use to impart color to the dietary ingredient or dietary supplement. Color additives are exempt from the definition of "food additive" under section 201(s)(3) of the act and subject to approval and listing under section 721 of the act.