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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 111 and 112

[Docket No. 96N-0417]

RIN 0910-AB88

Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing current good manufacturing practice (CGMP) regulations for dietary ingredients and dietary supplements. The proposed rule would establish the minimum CGMPs necessary to ensure that, if you engage in activities related to manufacturing, packaging, or holding dietary ingredients or dietary supplements, you do so in a manner that will not adulterate and misbrand such dietary ingredients or dietary supplements. The provisions would require manufacturers to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements. The proposed rule is one of many actions related to dietary supplements that we (FDA) are taking to promote and protect the public health.

DATES: Submit written comments by [insert date 90 days after date of publication in the FEDERAL REGISTER]. Submit written

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written comments on the collection of information by [insert date 30 days after date of publication in the FEDERAL REGISTER].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

Fax written comments on the information collection to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), Attn: Stuart Shapiro, Desk Officer for FDA, FAX 202-395-6974, or electronically mail comments to sshapiro@omb.eop.gov.

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I. Background

A. Dietary Supplement Health and Education Act (DSHEA)

DSHEA (Public Law 103-417) was signed into law on October 25, 1994. DSHEA, among other things, amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 402(g) (21 U.S.C. 342(g)). Section 402(g)(2) of the act provides, in part, that the Secretary of Health and Human Services (the Secretary) may by regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after CGMP regulations for food and may not impose standards for which there is no current and generally available analytical

methodology. No standard of CGMP may be imposed unless such standard is included in a regulation issued after notice and opportunity for comment in accordance with 5 CFR chapter V.

Congress enacted DSHEA to ensure consumers' access to safe dietary supplements. In the findings accompanying DSHEA, Congress stated that improving the health status of U.S. citizens is a national priority and that the use of dietary supplements may help prevent chronic diseases and maintain good health (Ref. 1). If dietary supplements are adulterated because they contain contaminants (such as filth), because they do not contain the dietary ingredient they are represented to contain (for example, a product labeled as vitamin C that actually contains niacin), or because the amount of the dietary ingredient thought to provide a health benefit (for example, folic acid to reduce the risk of neural tube defects or calcium in an amount to reduce the risk of osteoporosis) is not actually present in the supplement, then the consumer may suffer harm or may not obtain the purported health benefit from their consumption. CGMP regulations for dietary ingredients and dietary supplements will help to ensure that the potential health benefits that Congress identified as the basis for DSHEA are obtained and that consumers receive the dietary ingredients that are stated on the product label.

DSHEA directed the President to appoint a Commission on Dietary Supplement Labels (the Commission) to consider several

issues under DSHEA needing clarification. The Commission was to conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims. In making its recommendations, the Commission was to evaluate how best to provide truthful, scientifically valid, and nonmisleading information to consumers so that such consumers could make informed and appropriate health care choices for themselves and their families. The Commission's report (Ref. 80) states that the Commission supports the efforts of industry and FDA to develop appropriate CGMPs for dietary supplements. Guidance on the type of information that a responsible manufacturer should have to substantiate statements of nutritional support and safety is also included in the Commission's report. The Commission's report states that the substantiation files should include assurance that CGMPs were followed in the manufacture of the product.

B. The Advance Notice of Proposed Rulemaking

On November 20, 1995, representatives of the dietary supplement industry submitted to FDA an outline for CGMP regulations for dietary supplements and dietary supplement ingredients. We evaluated the outline and determined that it provided a useful starting point for developing CGMP regulations.

Nonetheless, we believed that the industry outline did not address certain issues that should be considered when developing a proposed rule on CGMPs for dietary ingredients and dietary supplements. For example, the industry outline did not address the need for specific controls for automatic, computer-controlled or assisted systems.

In addition to identifying a number of issues that were not included in the industry outline but on which we wanted public comment, we also recognized that other interested parties, such as consumers, other industry segments who had not participated in developing the outline, and the health care community should have an opportunity to provide comments on CGMPs for dietary supplements before we developed a proposal. Therefore, in the FEDERAL REGISTER of February 6, 1997 (62 FR 5700), we issued an advance notice of proposed rulemaking (ANPRM) asking for comments on whether to institute rulemaking to develop CGMP regulations for dietary ingredients and dietary supplements and what would constitute CGMP regulations for these products.

The ANPRM contained the entire text of the industry outline. We also asked nine questions (which we discuss later in section II.B of this document) in the ANPRM. The questions focused on issues that the industry outline did not address such as those issues noted above. We received approximately 100 letters in response to the ANPRM. Each of those letters contained one or

more comments. The comments came from consumers, consumer advocacy groups, health care professionals, health care professional organizations, industry, and industry trade associations. The majority of comments responded both to the nine questions we asked in the ANPRM and on certain provisions in the industry outline. We also address the comments on the nine questions in section II.B of this document. We discuss significant comments about certain provisions in the industry outline in our discussion of related proposed requirements.

Included with its comments to the ANPRM, the United States Pharmacopeia (USP) submitted a copy of its general chapter, "Manufacturing Practices for Nutritional Supplements," (Ref. 2) and in March/April 2002, USP proposed revisions to this general chapter to introduce provisions pertaining to botanical preparations (Ref. 82). In February 2000, we received a copy of the National Nutritional Foods Association's (NNFA) "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" (Ref. 3). We found that the industry outlines published in the ANPRM, the USP manufacturing practices, and the NNFA standards were useful in developing this proposed rule. We included certain provisions found in these outlines in this CGMP proposed rule. These three outlines indicate that dietary ingredient and dietary supplement manufacturers already recognize that there are basic, common steps needed to

manufacture a dietary ingredient or dietary supplement that is not adulterated although, as established in the regulatory impact analysis, a large percentage of manufacturers do not follow a good manufacturing model. For example, these practices include requirements for:

- Designing and constructing physical plants that facilitate maintenance, cleaning, and proper manufacturing operations or to prevent mixup between different raw materials and products;
- Establishing a quality control unit;
- Establishing and following written procedures for:
    1. Maintaining and cleaning equipment and utensils;
    2. Receiving, testing, or examining materials received and testing of finished product;
    3. Using master and batch control records;
    4. Handling consumer complaints; and
    5. Maintaining records for laboratory tests, production control, distribution, and consumer complaints.

Based on the ANPRM, the comments that we received in response to the ANPRM, our outreach activities (which we discuss below), and our own knowledge and expertise about CGMPs for foods, drugs, cosmetics, devices, and biologics, we are proposing to establish these CGMP regulations for dietary ingredients and dietary supplements. The proposed regulations would impose

requirements for: (1) Personnel, (2) physical plants, (3) equipment and utensils, (4) production and process controls, (5) holding and distributing, (6) consumer complaints related to good manufacturing practices, and (7) records and recordkeeping.

C. Industry and Consumer Outreach

During 1999, we conducted a number of outreach activities related to dietary supplements. We held several public meetings to obtain input from the public on developing our overall strategy for achieving effective regulation of dietary supplements, which could include establishing CGMP regulations. We also held public meetings focused specifically on CGMPs and the economic impact that any CGMP rule for dietary ingredients and dietary supplements may have on small businesses. Additionally, FDA staff toured several dietary supplement manufacturing firms to better understand the manufacturing processes and practices that potentially would be subject to a CGMP regulation for dietary ingredients and dietary supplements. Each of these activities contributed to our knowledge about the industry.

1. Dietary Supplement Strategic Plan Meetings

We held public meetings on June 8 and July 20, 1999, to collect stakeholder comments on the development of our overall strategy for achieving effective regulation of dietary supplements. We designed the meetings to provide an opportunity

for public comment on both the activities we should undertake as part of an overall strategy and the prioritization of those activities. In the notices for these meetings, we identified the development of CGMPs for dietary supplements as one activity that should be considered in an overall strategy.

During and after the strategic meetings, we received comments from consumers, consumer advocacy groups, health care professionals, health care professional organizations, industry, and industry trade associations. The comments addressed a wide range of activities related to regulating dietary supplements. (These comments can be seen at our Dockets Management Branch (see ADDRESSES) in docket number 99N-1174.) The comments generally identified the development of CGMP regulations as a high priority activity that should be included in any FDA strategic plan for regulating dietary supplements. Some comments that addressed the development of CGMPs are summarized as follows:

- It would be useful to industry to have FDA establish CGMPs especially for small and intermediate-size firms that are not clear on what they should be doing;
- CGMPs would establish a level playing field for industry, which would help prevent irresponsible firms from making and selling adulterated products;
- CGMPs should be able to accommodate a wide variety of firms, that is, small and large firms that manufacture

a wide array of different types of products and ingredients;

- CGMPs should ensure that consumers get dietary supplements with the strength and the purity that consumers expect;
- CGMPs should ensure that every dietary supplement on the market has the safety, identity, purity, quality, and strength it purports in the label to possess;
- CGMPs should include ingredient identity testing and other testing;
- CGMPs should ensure that dietary supplements are produced using a master formula procedure and produced in a sanitary facility;
- CGMPs should require that manufacturers have documented evidence that their manufacturing process is under control on a consistent basis;
- CGMPs should require manufacturers to test dietary ingredients, particularly imported botanicals, for heavy metals, pesticides, and industrial contaminants;
- CGMPs should require expiration dating and testing for dissolution and bioequivalence;
- CGMPs should require that companies report adverse reactions; and

- CGMPs should include guidance on testing for ingredient identity and adulteration with toxic substances.

2. Small Business Outreach Meetings

We held public meetings on July 12, September 28, and October 21, 1999, to collect information from industry and others that would help us to understand the economic impact on small businesses of CGMP regulations for dietary supplements. Transcripts of these public meetings (docket number 96N-0417, "Development of Strategy for Dietary Supplements") are available at our Dockets Management Branch or electronically at http://www.fda.gov/ohrms/dockets/dockets/96n0417/tr00001.pdf. Public comments from small businesses included both support of and concern for CGMP regulations. Small businesses expressed concerns about the cost and the time involved in complying with any rule that contains the following requirements:

- Conducting tests to determine identity, purity, quality, strength, and composition of dietary ingredients and dietary supplements;
- Maintaining written procedures and records documenting that procedures are followed; and
- Providing data that support expiration dating.

Public comments from small business expressed support for dietary supplement CGMP regulation. Some small businesses (1 with 15 employees) commented that they have CGMPs in place with written

procedures tailored to the size of their operations. One small business with sales under $1 million commented that their plant materials received in fresh form are identified onsite by a botanist, and when the onsite botanist is not able to confirm identity, the plant material is sent to an outside laboratory that conducts chemical analysis to confirm identity.

3. Site Visits to Dietary Supplement Manufacturing Firms

During the summer and fall of 1999, we visited eight dietary supplement manufacturing firms. These visits included firms that: (1) Manufacture a vitamin using a fermentation process; (2) grind, sift, blend, and otherwise treat raw agricultural commodities (e.g., botanicals); (3) manufacture dietary ingredients for use in manufacturing dietary supplement tablets, capsules, softgels, and powders; (4) manufacture dietary supplements for packaging and labeling by others; and (5) manufacture, package, and label dietary supplements under their own and others' labels. The firms varied in size and were located in several parts of the country.

We found an array of manufacturing, packaging, and holding practices in the firms. The practices included the following:

- Using CGMPs similar to those included in the ANPRM;
- Using automatic systems to quarantine, segregate, approve, and release inventory;
- Following written procedures;

- Having quality control units with the responsibility and authority outlined in the ANPRM;
- Performing one or more tests on dietary ingredients and dietary supplements to determine the identity, purity, quality, strength, and composition;
- Verifying the reliability of suppliers' certifications; and
- Documenting and maintaining records for certain procedures, such as master and batch production, quality control and laboratory operations, distribution, and processing consumer complaints.

D. Food Advisory Committee Report

In February 1998, the Food Advisory Committee (FAC) established a Dietary Supplement Working Group to consider what constitutes adequate testing for identity of different dietary ingredients and what records are necessary to demonstrate that CGMPs are maintained throughout the manufacturing and distribution process. The working group issued a report that discussed the selection of the most appropriate and reliable identity test and the general principles for consideration in setting performance standards for such tests (Ref. 4). The report also identified the types of records that would be necessary to demonstrate that CGMPs are maintained throughout the manufacturing and distribution process. On June 25, 1999, the

working group presented its report, in draft form, during an FAC public meeting. We received public comments during and after the June 25, 1999, public meeting.

Although this proposal does not address dietary ingredient identity testing in the same detail as the working group's report, we considered the report in developing requirements for identity testing and CGMP records requirements in this proposal. The working group's report may be useful in developing industry guidance to supplement a CGMP regulation for dietary ingredients and dietary supplements. We discuss dietary ingredient and dietary supplement identity testing and recordkeeping for CGMP proposed requirements in more detail later in this document.

E. FDA's Decision to Propose a Rule

This proposed regulation, which sets forth proposed CGMPs for dietary ingredients and dietary supplements, is part of our overall strategy for regulating dietary supplements in a manner that promotes and protects the public health. Before drafting the proposal, FDA considered public comment in response to the ANPRM and to public meetings, observations at site visits to dietary supplement manufacturers, and advisory group reports. In drafting this proposal, FDA used, in part, the industry coalition outline that was published as an ANPRM (62 FR 5700) in which the industry adopted broad provisions beyond those found in part 110 (21 CFR part 110). FDA's purpose at this proposed rule stage is

to present a broad enough scope so that it may receive comment on the depth and breadth of what should be considered by the agency in developing a final rule. Our intent is to provide the proper balance of regulation so that dietary ingredients and dietary supplements are manufactured in a manner to prevent adulteration using recognized scientific principles and both industry and consumer expectations that are reasonable and appropriate. Therefore, FDA seeks comment on whether each of the proposed provisions are necessary to ensure the safety and quality of dietary ingredients and dietary supplements and whether they are adequate to protect the public health. In addition, we seek comment on whether there are certain provisions that are not proposed but that may be necessary. Comments should include justification for why provisions may or may not be necessary, including supporting data where appropriate. If comments assert that certain provisions are not necessary, comments should include an explanation on how, in the absence of the requirement, one can ensure that there would be adequate protection of the public health when there is risk of adulteration. Comments also should address whether the gains to consumers in product safety and quality are warranted. Moreover, assuming that this proposal does advance the public health, comments should address whether there is any reason to apply different requirements, including greater or lesser requirements on small firms as

compared to larger firms and the rationale for doing so. Finally, comments should address the agency's legal authority to issue these regulations.

In deciding whether to propose CGMP regulations for dietary supplements, we asked ourselves:

- Why are CGMP regulations needed?
- How will CGMP regulations take into account technical feasibility? and
- How can FDA help industry achieve compliance with CGMPs?

1. Why Are CGMPs Needed?

CGMP regulations for dietary ingredients and dietary supplements are necessary to promote and protect the public health. In addition, CGMP regulations would benefit consumers economically and would benefit industry.

a. CGMPs help protect the public health. The dietary supplement industry is one of the fastest growing product areas that FDA regulates. In 1999, Prevention magazine conducted a survey entitled "Consumer Use of Dietary Supplements" (Ref. 5). The survey used data from telephone interviews with a nationally-representative sample of 2,000 adults living in households with telephones in the continental United States. The telephone interviews were done in April and May, 1999. Using population estimates based on the Census Bureau's March 1998 Current

Population Survey Estimates, the survey stated that approximately 186,014,712 adults live in the households with telephones in the United States and that an estimated 158.1 million of these Americans in households with telephones use dietary supplement products. These consumers spend approximately $8.5 billion a year on dietary supplements. The survey also found that:

- Only 41 percent of the surveyed consumers who use vitamins and minerals think they are very safe and only 50 percent think they are somewhat safe;
- Only 24 percent of the surveyed consumers who use herbal products think they are very safe; and only 53 percent think they are somewhat safe; and
- Twelve percent of the surveyed consumers who have used dietary supplements say they have experienced side effects or adverse reactions from their use of dietary supplements.

The survey also found strong public support for increased Government regulation of dietary supplements; 74 percent of the surveyed consumers reported that they think that the Government should be more involved in ensuring that these products are safe and do what they claim to do.

However, unlike other major product areas, there are no FDA regulations that are specific to dietary ingredients and dietary supplements that establish a minimum standard of practice for

manufacturing, packaging, or holding. The absence of minimum standards has contributed to the adulteration and misbranding of dietary ingredients and dietary supplements by contaminants or because manufacturers do not set and meet specifications for their products, including specifications for identity, purity, quality, strength, and composition. Thus, CGMP regulations are necessary to protect the public health because a CGMP rule would establish a minimum standard of practice for manufacturing, packaging, and holding dietary ingredients and dietary supplements.

The following examples illustrate the wide range of dietary ingredient and dietary supplement adulteration caused by manufacturing, packaging, or holding practices. The examples, although not exhaustive, demonstrate why CGMPs are necessary to protect public health:

- In 1997, we received an adverse event report (AER) regarding a young woman who had taken a dietary supplement and experienced a life-threatening abnormal heart function (Ref. 6). We investigated the AER and determined that the dietary supplement the woman consumed contained Digitalis lanata, a plant that can cause life-threatening heart reactions (Refs. 6 through 10). We found D. lanata in samples of raw material labeled "plantain" that was a dietary ingredient in one

of the dietary supplement products used by this woman (Ref. 6). A nationwide listing of manufacturers indicated that 183 firms may have used the contaminated dietary ingredient in dietary supplements. The proposed CGMP regulations, had they been in effect, would have required identity and purity tests of dietary ingredients and dietary supplements and would likely have prevented the use of the D. lanata in these dietary supplements.

- In 1998, the American Herbal Products Association (AHPA) surveyed its members about commonly adulterated botanicals and methods useful in detecting adulteration in botanicals (Ref. 11). AHPA members identified 43 botanicals, including D. lanata contaminated plantain, that are commonly adulterated with contaminants, the common adulterant for each botanical, and a method for identifying the adulterant. For example, aflatoxin and mycotoxin (toxic compounds produced by certain molds) are known to contaminate certain herbal and botanical dietary supplements (Refs. 11 through 14). Under this proposed rule, a manufacturer would have to establish specifications for botanicals that may contain toxic compounds and conduct testing to ensure that there are

not toxic compounds present that may adulterate the dietary ingredient or dietary supplement.

- We have found manufacturers using nonfood-grade chemicals to manufacture dietary supplements (Ref. 15). The proposed rule would require that manufacturers establish specifications for components used in manufacturing and also would require manufacturers to establish and follow laboratory control procedures that include criteria for establishing appropriate specifications. The proposal would further require manufacturers to conduct testing to confirm that their specifications are met. These requirements, if finalized, would ensure that manufacturers establish and use appropriate criteria, such as using food-grade rather than industrial-grade chemicals, and would ensure that manufacturers conduct testing to confirm that food-grade chemicals were received from the supplier.
- Also during inspections, we have found insanitary conditions in physical plants where dietary ingredients or dietary supplements were manufactured, packaged, or held (Ref. 16). Pest infestation, building and equipment defects, and leaking pipes that drip onto dietary supplements are examples of insanitary

conditions that we have found that may lead to product adulteration and could cause consumer illnesses and injuries. The proposed rule would require a manufacturer, packager, or holder to maintain its physical plant used for these activities in a sanitary condition.

- In the past, we have been involved in the recall of dietary supplements contaminated with lead (Ref. 17), salmonella (Ref. 18), Klebsiella pneumonia (Ref. 19), botulism (Ref. 20), and glass (Ref. 21). These contaminants can cause serious illness or injury and, in the case of lead, may result in chronic irreversible cognitive defects in children and progressive renal failure in adults. The proposed rule would require dietary ingredients and dietary supplements to be manufactured, packaged, and held in a manner that prevents adulteration, including adulteration by the contaminants such as those described.
- We also have been involved in recalls for super- and subpotent dietary supplements. Recalls of superpotent dietary supplements have included the following dietary ingredients: Vitamin A (Ref. 22), vitamin D (Ref. 23), vitamin B6 (Ref. 24), and selenium (Ref. 25). Each of these dietary supplements contained dietary ingredient

levels that could have caused serious illness or injury. Illnesses or injuries such as nausea, vomiting, liver damage, and heart attack were reported from superpotent niacin at an average level of 452 milligrams (mg) niacin, well above the upper limit for adults of 45 mg daily (Ref. 26). Recalls for subpotent dietary supplements have included a recall of folic acid because the dietary supplement contained 34 percent of the declared level (Ref. 27). Such a product would be misbranded under section 403 of the act (21 U.S.C. 343). Folate plays a well-documented and important role in reducing the risk of neural tube defects. Neural tube birth defects, primarily spina bifida and anencephaly, cause serious lifetime debilitating injuries and disabilities, and even death. Thus, use of subpotent folic acid by women who are or may become pregnant may result in increased risk of having a child with a neural tube defect. The proposed rule would require manufacturers to establish specifications for the dietary supplement the manufacturer makes and then meet those specifications. Therefore, if the proposed rule is finalized, if the label for a folic acid supplement declares that the dietary supplement contains a certain level of folic

acid, the folic acid supplement must actually contain that level, or we would consider the folic acid supplement to be adulterated under section 402(g) of the act.

- Other recalls have been necessary because of undeclared ingredients, including color additives (Refs. 28 and 29), lactose (Ref. 30), and sulfites (Ref. 31). Undeclared ingredients, such as color additives, lactose, and sulfites, may cause potentially dangerous reactions in susceptible persons (Ref. 32). The proposed rule would require manufacturers to verify that the correct labels have been applied to dietary ingredients and dietary supplements produced. The master manufacturing record would have to identify each ingredient required to be declared on the ingredient list under section 403 of the act.
- A study found that dietary ingredient content varied considerably from the declared content (Ref. 33). The study examined ephedra alkaloids in 20 herbal dietary supplements containing ephedra (Ma Huang) to determine their ephedra alkaloid content. This study found that norpseudoephedrine was often present in the ephedra dietary supplements. The study also observed significant lot-to-lot variations in alkaloid content

for four products, including one product that had lot-to-lot variations of ephedrine, pseudoephedrine, and methylephedride that exceeded 180 percent, 250 percent, and 1,000 percent, respectively. Half of the products tested differed in their label claims for ephedra alkaloid content and their actual alkaloid content. In some cases, the discrepancy exceeded 20 percent. One product did not have any ephedra alkaloids. Lot-to-lot variation in dietary ingredients is a public health problem particularly because conditions of use recommended or suggested in the labeling of dietary supplements are presumably based on the dietary supplement containing a certain amount of the dietary ingredient. If the dietary supplement contains more or less than the amount that the manufacturer represents, then the consumer does not receive the potential health benefit from the dietary supplement or is exposed to an amount that could present risk of injury or illness. The proposed rule would require manufacturers to establish controls, including master manufacturing and batch production records to ensure that they use the correct amount of the dietary ingredient to produce the dietary supplement, and that they apply the correct label to the dietary supplement.

- A private company analyzed a sample of dietary supplements and found that some dietary supplements did not contain the dietary ingredients claimed on the label (Ref. 34). The study found that 25 percent of gingko biloba products, 20 percent of saw palmetto, 33 percent of glucosamine, chrondroitin and combined glucosamine/chondroitrin, and 50 percent of SAMe did not contain the dietary ingredients claimed in their product labels. The proposed rule would require manufacturers to establish and meet specifications for the identity, purity, quality, strength, and composition of dietary supplements.

Given the wide range of public health concerns presented by the manufacturing, packaging, and holding practices for dietary ingredients and dietary supplements, a comprehensive system of controls is necessary to prevent adulteration and misbranding. CGMPs are intended to establish such a comprehensive system. Manufacturers who operate in accordance with CGMPs would be less likely to distribute adulterated and misbranded dietary ingredients or dietary supplements than those who do not meet the requirements. Quality assurance will maximize the probability that unadulterated dietary supplements will reach the marketplace.

Establishing CGMP regulations for dietary supplements is only part of our broad science-based regulatory program for dietary supplements that is necessary to give consumers a high degree of confidence in the safety, composition, and labeling of dietary supplements. Aside from our CGMP efforts, we have taken other steps to protect the public health, such as:

- Reviewing claim notifications under section 403(r)(6) of the act to identify unlawful claims;
- Reviewing new dietary ingredient notifications to ensure that new dietary ingredients are reasonably expected to be safe under section 413 of the act (21 U.S.C. 350b);
- Evaluating the nutrition labeling of dietary supplements;
- Monitoring, through AERs voluntarily submitted to FDA, the occurrence of adverse events to identify potentially unsafe products; and
- Taking compliance actions against products that are adulterated or misbranded.

The CGMP regulation, if finalized, would, along with our other dietary ingredient and dietary supplement initiatives, contribute further to the protection of public health.

b. CGMPs benefit consumers. In addition to the public health benefits for consumers, CGMP regulations for dietary

ingredients and dietary supplements will benefit consumers in other ways. Consumers should not have to wonder whether the dietary supplements they buy are adulterated or whether they contain the correct dietary ingredients or contain the dietary ingredients in the amount stated on the product's label. Consumers who purchase a product that does not contain the amount or strength listed on the label experience an economic loss because they are paying for something that they did not receive. CGMPs would require manufacturers to establish and meet specifications for identity, purity, quality, strength and composition of dietary supplements to help ensure that consumers buy dietary supplements that are not adulterated, contain the dietary ingredients declared on the product's label, and contain the amount or strength listed on the label. Therefore, CGMPs would benefit consumers.

2. How Will CGMP Regulations Take Into Account Technical Feasibility?

In developing this proposed rule, we were careful not to propose requirements that are not technically feasible to meet. In some areas where there has been scientific study but where the science is still evolving, the proposal recognizes the evolving state of the science, but would give you maximum flexibility in meeting the requirement. For example, there are tests available for identity, purity, quality, strength, and composition of

certain dietary ingredients or dietary supplements. Because many tests for identity, purity, quality, strength, and composition of dietary ingredient or dietary supplements have not been officially validated, the proposal would permit tests using methods other than those that are officially validated. By using the term "officially validated," we mean that the method is validated using an interlaboratory collaborative study by which a proposed method is validated by independent testing in separate laboratories under identical conditions (Ref. 35). An AOAC International (formerly the Association of Official Analytical Chemists) Official Method is an example of an officially validated method. We discuss test methods validation in more detail later in this document.

In areas where scientific study is still evolving, we did not propose specific requirements. For example, we did not propose requirements for dissolution, disintegration, bioavailability, or expiration dating. In those areas, it may be premature to propose a requirement at this time. In the preamble to this rule, we identify those areas where additional scientific study is necessary before we can propose a dietary supplement CGMP requirement. For example, we did not identify defect action levels (DALs) for dietary ingredients because there are not enough data available to identify an appropriate DAL for most dietary ingredients. Likewise, further study is needed for some

dietary ingredients before dissolution, disintegration, bioavailability, expiration dating, or other quality standard requirements can be proposed.

3. How Can FDA Help Industry Achieve Compliance With CGMPs?

During small business outreach public meetings and in comments to the ANPRM, members of the dietary supplement industry told us that they would like our help in determining how to implement CGMP regulations for dietary ingredients and supplements. We have heard that issuing guidance documents and education and training would be helpful. We invite comment on the use of guidance documents, education, training, or other approaches and potential sources of education and training that you believe would assist industry efforts to implement the proposed CGMP regulations, if finalized as proposed.

F. Proposal Highlights and Requests for Comments

This proposed rule is intended to ensure that manufacturing practices will not result in an adulterated dietary supplement and that supplements are properly labeled. This proposed rule, if finalized as proposed, will give consumers greater confidence that the dietary supplements they choose to use will have the identity, strength, purity, quality, or composition claimed on the label. A manufacturer of a dietary ingredient or a dietary supplement cannot make claims that state or imply that the dietary ingredient or dietary supplement is safe and/or effective

simply because it has been manufactured in compliance with current good manufacturing practice (CGMP) requirements. However, we believe that a voluntary labeling statement about the fact that a dietary ingredient or dietary supplement has been made in compliance with CGMP requirements might be made lawfully under the act, provided that such a statement is made in an appropriate context and with adequate disclaimers so that consumers fully understand it and are not misled by it. The proposed rule governing CGMP requirements for dietary supplements address manufacturing controls to ensure that dietary ingredients and dietary supplements are produced in a manner that will not adulterate or misbrand such products. Compliance with any final rule, based on the proposal, will not ensure that the dietary ingredient or dietary supplement itself is safe or effective. Thus, the agency believes that an unqualified statement saying simply "produced in compliance with dietary supplement current good manufacturing practice requirements," without more, could well suggest that a product may be safe and effective or somehow superior to other dietary ingredient and dietary supplement products that are subject to the same CGMP requirements. Such a statement would likely be considered misleading by FDA under sections 403(a)(1) and 201(n) of the act. We believe however, that it might be possible to cure an unqualified statement by including language clarifying to consumers that all dietary

ingredients and dietary supplements must be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary ingredient or dietary supplement is safe or effective. As usual, the manufacturer would be responsible for ensuring that any such voluntary labeling statements on its dietary ingredient and dietary supplement products are truthful and not misleading. The agency would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

We propose requirements for: (1) Personnel, (2) the physical plant environment, (3) equipment and utensils, (4) production and process controls, (5) holding and distributing, (6) consumer complaints related to CGMPs, and (7) records and recordkeeping. Key provisions of the proposed rule are highlighted below. We also seek comment on whether certain additional provisions should be included as requirements in a final rule.

Proposed "personnel" requirements would require that you have qualified employees and supervisors, to take measures to exclude any person from your operations who might be a source of microbial contamination, and to use hygienic practices to the extent necessary to protect against contamination.

Proposed "physical plant" requirements are intended to help prevent contamination from your physical plant environment. You

would be required to design and construct your physical plant in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding. You would be required to 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.

Proposed "equipment and utensils" provisions would require that you use equipment and utensils that are of appropriate design, construction, and workmanship for their intended use and that you provide for adequate cleaning and maintenance. You would be required to maintain and calibrate your instruments and controls for accuracy and precision and to ensure that automatic, mechanical, and electronic equipment works as intended. You would also be required to maintain, clean, and sanitize, as necessary, all equipment utensils and contact surfaces that are used to manufacture, package, or hold dietary ingredients or dietary supplements.

Under the proposed "production and process controls" requirements, you would be required to establish and use a quality control unit in your manufacturing, packaging, and label operations. We propose requirements for establishing and using master manufacturing records and batch control records to ensure batch-to-batch consistency. Specifications would be required for

any point, step, or stage in the manufacturing process where control is necessary to ensure that the dietary supplement contains the identity, purity, quality, strength, and composition claimed on the label. We propose flexible testing requirements: You would be required to test final products for adherence to specifications, unless a scientifically valid analytical method does not exist; in the latter case, you would be required to test incoming shipment lots of components, dietary ingredients, or dietary supplements for any such specification, and to test in-process for any such specification in accordance with the master manufacturing record where you determine control is necessary to ensure the identity, purity, quality, strength, and composition of the product.

Proposed "holding and distributing" requirements would protect components, dietary ingredients, dietary supplements, packaging, and labels against contamination and deterioration. You would be required to hold components, dietary ingredients, dietary supplements, packaging, and labels under appropriate conditions of temperature, humidity, and light so that their quality is not affected; and under conditions that do not lead to the mixup, contamination, or deterioration.

Proposed "consumer complaints" requirements would require that you keep a written record of each consumer complaint related to good manufacturing practices; review such complaints to determine whether the consumer complaint involves a possible

failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any other requirements of this part, including those that may result in a possible risk of illness or injury (i.e., an adverse event); and investigate a consumer complaint when there is a reasonable possibility of a relationship between the consumption of a dietary supplement and an adverse event. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. 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.

Proposed "records and recordkeeping" requirements would tell you how long you must keep certain records to show how you complied with the CGMP requirements. We would require that you keep written records for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with those records and have all required records, or copies of such records, readily available during the retention period for authorized inspection and copying by FDA when requested.

CGMP records document the manufacturer's operation throughout time and are essential to an enforceable regulation. Because FDA does not observe the manufacturer's operation

fulltime, records can ensure that the FDA has the information needed to identify noncompliance and to bring a non-compliant manufacturer into compliance. Records can show that appropriate monitoring is performed, pinpoint with confidence when a deviation began and ended, and prove that required quality control measures and practices were performed as often as necessary to ensure control. Review of manufacturing records with sufficient frequency can ensure that any problems are uncovered promptly and can facilitate prompt modification, have an impact on the production of subsequent batches of the product, and prevent introduction of potentially hazardous dietary supplements into the market place. Review of consumer complaint records can facilitate the identification of trends in reports of illness or injury, identify related batch records to identify previously undetected manufacturing deviation, and have an impact on the prompt recall of any potentially hazardous dietary supplement.

We seek comment on whether the proposed recordkeeping requirements are not necessary to prevent adulteration; to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement; to an enforceable regulation; and for the other reasons cited. If comments assert that recordkeeping provisions are not necessary, comments should include an explanation of why recordkeeping requirements are not

necessary including how, in the absence of the requirements, one can prevent adulteration, ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement, ensure an enforceable regulation, and the other reasons cited. If comments agree that the recordkeeping requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

Although records are not required in 21 CFR Part 110, CGMPs in manufacturing, packing, or holding human food, records are required in the other commodity-driven food CGMPs (i.e., 21 CFR Part 129, Processing and bottling of bottled drinking water; 21 Part CFR 120, Hazard Analysis and Critical Control Point (HAACP) Procedures for the Safe and Sanitary Processing and Importing of Juice; 21 CFR Part 123, Fish and fishery products; 21 CFR Part 106 Infant formula quality control procedures; and 21 CFR Part 113, Thermally processed low-acid foods packaged in hermetically sealed containers). Further, records are included in the CGMPs submitted to FDA by industry, the National Nutritional Foods Association Standards, the NSF International draft standards (Ref. 83), and the USP draft Manufacturing Practices for Dietary Supplements.

We seek comment on whether certain additional provisions should be included as requirements in a final rule. For example,

we invite comment on whether a final rule should include a requirement for certain personnel records; for written procedures in a number of areas; for equipment verification; and for expiration dating and related testing. Written procedures are included in the dietary supplement CGMP outline submitted to FDA by industry, National Nutritional Foods Association standards, the NSF International draft standards, and the USP draft Manufacturing Practices. In order to limit the burden to manufacturers, FDA is not proposing to require written procedures. However, FDA is proposing that manufacturers maintain appropriate records to ensure the identity, purity, quality, strength, and composition of a given product and records that are necessary for efficient enforcement and to permit trace back. Although we have not proposed requirements for written procedures as did these other groups, we seek comment on whether such practices should be included in a final rule. Later in this document, we request comments on specific written procedures and describe FDA's current thinking concerning what could be included in such a written procedure.

We also seek comment on whether this rule should include specific requirements for the use of animal-derived dietary ingredients, and requirements for persons who handle raw agricultural commodities. Specific requests for comment of this type are contained below in relevant sections of this preamble.

II. General Issues

A. Legal Authority

We are proposing these regulations under sections 201, 393, 409, 701(a), 704, and 801 of the act (21 U.S.C. 321, 903, 348, 371(a), 374, and 381) and sections 402 and 403 of the act and section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264).

Section 402(g) of the act gives us explicit authority to issue a rule regulating conditions for manufacturing, packaging, and holding dietary supplements. Section 402(g)(1) of the act states that a dietary supplement is adulterated if "it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations." Section 402(g)(2) of the act authorizes us to, by regulation, "prescribe good manufacturing practices for dietary supplements." In addition, section 402(g)(2) of the act states that any such regulations "shall be modeled after current good manufacturing practice regulations for food and may not impose standards for which there is no current and generally available analytical methodology."

In section 402(g)(2) of the act, which describes the general parameters of CGMPs for dietary supplements, Congress stated that the regulations were to be "modeled after current good manufacturing practice regulations for food." To determine what

Congress meant, we look to the plain meaning of the phrase. Webster's II New Riverside University Dictionary defines "model" as "[a] preliminary pattern serving as the plan from which an item not yet constructed will be produced" (Ref. 81). Thus, when Congress used the term "modeled after" Congress intended that we use the food CGMPs as a "preliminary pattern" for the dietary supplement CGMPs. If Congress had intended for the agency to adopt food CGMPs as the CGMPs for dietary supplements, Congress could have explicitly stated that dietary supplements were subject to food CGMPs.

The provisions in the dietary supplement CGMP proposal are modeled after food CGMPs. The general CGMP provisions for food in part 110 relate not only to insanitary production practices, but other practices, such as having appropriate quality control operations, to ensure that a food is manufactured in a manner that will not adulterate the food. Further, the CGMPs in part 110 describe the minimally acceptable practices for all food handling operations. They are not intended to cover specific issues that may relate to a particular product type, rather, are general provisions concerned with practices relating to the receiving, inspecting, quality control operations, packaging, segregating, processing, storing, and transporting of food. The specific provisions of the food CGMPs are linked to hazards that

are inherent to foods (e.g., microbial contamination and contamination with macroscopic filth).

The proposed dietary supplement CGMPs are modeled after the food CGMPs in part 110 in that they cover the scope of practices related to the receiving, inspecting, quality control operations, packaging, segregating, processing, storing, and distribution of dietary ingredients and dietary supplements. Dietary supplements require many of the same types of sanitary practices and other practices as conventional food production in order to produce a product that is not adulterated; dietary supplements are subject to many of the same hazards as are conventional foods. However, dietary supplements have their own set of unique requirements as a result of the characteristics and hazards due to their "hybrid" nature, e.g., dietary supplements can be considered as falling somewhere along the continuum between conventional foods on the one hand and drugs on the other. Thus, the CGMPs for dietary supplements need to address the characteristics and hazards of dietary supplements, the operations and processes used to manufacture dietary supplements, particularly those necessary to ensure the identity, purity, quality, strength, and composition claimed on the label.

Dietary supplements, unlike conventional foods, contain ingredients that are consumed in very small quantities, for example, in a tablet or capsule. Such ingredients may be

intended to have an anticipated, specific physiological response. Such ingredients are more "drug-like" than "food-like," in part, because very small changes in the strength, purity, or quality of the ingredient can have significant, and possibly adverse, health consequences to those who ingest it. Thus, the dietary supplement CGMPs, by necessity, need to include provisions related to identity, purity, strength, quality, and composition of the product so that the dietary supplement "food" product will be manufactured in a manner that will not result in adulteration.

Further, plant products that are used to produce dietary supplements may be ground or in a powder and not easily recognized compared to conventional food that is readily identifiable (e.g., one can readily distinguish between white flour and white sugar, but not between ground plaintain and ground D. lanata). Thus, for the manufacturer to be sure that the dietary supplement contains the correct ingredient and the amount of the ingredient that is intended, the manufacturer must test or examine the ingredient using appropriate methods. The "modeled after" language in section 402(g) of the act provides the agency with the flexibility to devise CGMPs that make sense for dietary supplements, and that are based on the same principles as food CGMPs in part 110, i.e., to prevent adulteration related to insanitary conditions or other conditions that may be necessary to prevent adulteration, given the nature

of the specific food product and the characteristics of, and hazards inherent in, that food.

The scope of the legal authority for the proposed dietary supplement CGMPs includes the legal authorities upon which the food CGMPs are based. For example, section 402(a)(3) of the act states that a food is deemed adulterated if "it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food." Section 402(a)(4) of the act states that a food is deemed adulterated if "it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health." While section 402(a)(3) of the act focuses on the food itself, section 402(a)(4) of the act focuses on the conditions under which the food is prepared, packed, or held. Courts have adopted a broad reading of section 402(a)(4) of the act when we have taken actions to advance the public health (see U.S. v. Nova Scotia Food Products Corp., 568 F. 2d 240, 248 (2d Cir. 1977)). The agency tentatively concludes that the authorities that it relied on for its umbrella CGMPs in part 110 for food are relevant to the authorities that it needs for this proposed rule for dietary supplement CGMPs. In addition, section 409 of the act is another provision that is relevant to dietary supplement CGMPs. Section 409 of the act addresses circumstances under which a food may be deemed

adulterated based on the use of a food additive. Section 409 of the act is relevant to good manufacturing practices for foods, including dietary supplements, because a food would be deemed adulterated if it contained a food additive that was not used in a manner consistent with the statutory and regulatory requirements under section 409 of the act (see sections 402(a)(2)(C) and 409 of the act). Although Congress explicitly excluded "dietary ingredients," as defined in section 201(ff) of the act, from the definition of food additive, (see section 201(s)(6) of the act), ingredients other than dietary ingredients in a dietary supplement are subject to regulation as a food additive under section 409 of the act, unless they are subject to an exception to the definition of "food additive" under section 201(s) of the act.

Moreover, dietary ingredients and dietary supplements may contain pathogenic bacteria or viruses that pose serious public health and safety concerns (Ref. 36). Botanical dietary ingredients are living plants that may contain different microorganisms. These include Lactobacillus, Leuconostoc, Pseudomonas, and Xanthomonas species and molds. Potential pathogens such as Listeria monocytogens, Pseudomonas aeruginosa and Enterobacteriacae may also be present. Secondary microbial contamination from soil (Bacillus cereus, Clostridium perfringens and mycotoxin-producing molds, etc.), animal feces (Salmonella

and Shigella spp., Escherichia coli) and handling (Staphylococcus aureus) can also occur during harvesting, processing, and transportation (Ref. 36). Animal-derived dietary ingredients or dietary supplements may also pose a risk. For example, bovine colostrum, the lacteal secretion which precedes milk after a cow gives birth, is a substance that is used in dietary supplements and 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 or undulant fever. Glands and other animal tissues may contain the infective agent that causes transmissible spongiform encephalopathy (TSE) if they originate from an animal infected with the disease (Ref. 37).

We have authority to issue regulations under section 361 of the PHS Act. The Secretary delegated authority to the Commissioner of FDA (the Commissioner) to exercise the functions vested in the Secretary under section 361 of the PHS Act (see 21 CFR 5.10(a)(3)). This authority authorizes the Commissioner to issue and enforce regulations that, in the Commissioner's judgment, are necessary to prevent the introduction, transmission, or spread of communicable diseases from one State to another. Because this authority is designed to eliminate the introduction of diseases from one State to another, the Commissioner may exercise the authority over the disease-causing substance within the State where the food is manufactured,

packaged, or held. The Commissioner, therefore, assumes the authority to issue regulations under the PHS Act to assure that foods are manufactured, packaged, and held under conditions that will prevent the introduction, transmission, or spread of communicable diseases between States. Thus, the agency is invoking its authority under the PHS Act in this proposed rule to prevent the spread of communicable disease from dietary ingredients or dietary supplements in intrastate and interstate commerce.

In developing proposed CGMPs for dietary supplements, we relied on the basic concept underlying the food CGMPs and upheld by the courts. As a result, the basic concept for the food CGMPs and the proposed dietary supplement CGMPs is the same: To establish regulations that will help ensure that your practices for preparing, packaging, and holding dietary ingredients and dietary supplements do not result in an adulterated food entering interstate commerce.

In addition to relying on the broad authority in relevant sections of the act that we used to issue the food CGMP regulations, we look to the other relevant statutory language in section 402(g) of the act and the act as a whole in deciding the basis for our legal authority in proposing regulations related to the manufacture, packaging, and holding of dietary ingredients and dietary supplements. We note that certain terms Congress

used in section 402(g)(2) of the act, i.e., "standards" and "current and generally available analytical methodology," show that Congress intended to give us the authority to establish regulations in this rule that do not have parallel provisions in other food CGMPs. Specifically, the second phrase of the second sentence in section 402(g)(2) of the act states that we "may not impose standards for which there is no current and generally available analytical methodology." "Standards" and "current and generally available analytical methodology" are terms of art in the scientific field, and we are relying on the meaning of these terms in the field of science in these proposed CGMPs regulations, which implement that provision. This statutory language does not limit CGMPs for dietary supplements solely to the food CGMP regulations at the time DSHEA was enacted. If Congress had intended for the CGMPs for dietary supplements to be identical to the CGMPs for food, the language in section 402(g)(2) of the act relating to "standards" and "current and generally available analytical methodolog[ies]" would be meaningless. Thus, CGMP regulations for dietary ingredients and dietary supplements may include provisions relevant to dietary ingredients and dietary supplements that were not in current food regulations at the time DSHEA was enacted.

In addition to the broad authority in section 402(g) of the act, we look to the statutory scheme of DSHEA as a whole in

proposing regulations related to the manufacture, packaging and holding of dietary ingredients and dietary supplements. Section 403(q)(5)(F) of the act (section 7(b) of DSHEA) requires that a dietary supplement product provide nutrition information. To comply with section 403(q)(5)(F) of the act, you must be able to identify the dietary ingredient or ingredients in a dietary supplement and the quantity of each. Moreover, the provisions in section 403(s) of the act relate to identity, purity, quality, strength, and compositional specifications of a dietary supplement. Thus, Congress sought to ensure in DSHEA that dietary supplements would provide accurate information to the consumer on the identity of the dietary ingredient and, if an herb or botanical, the source from which it is derived. Moreover, Congress sought to ensure that the dietary supplement would have the strength or meet the quality, purity, and compositional specifications that the dietary supplement is represented to meet. Because Congress established section 403(s) of the act--a provision that requires that a dietary supplement that bears representations about identity, purity, quality, strength, and compositional specifications meet those representations--it is reasonable for us to establish regulations for manufacturing, packaging, and holding addressing those same features. These representations relate to characteristics and hazards to which dietary supplements are subject. Further, in

section 402(f) of the act, Congress identified circumstances under which a dietary supplement or a dietary ingredient would be deemed adulterated because it may present a significant or unreasonable risk of illness or injury. Congress expected that a dietary supplement would be manufactured in a way that ensures that the dietary supplement contains dietary ingredients that do not present an unreasonable risk of illness or injury and for which the conditions of use are based. Because one must be able to measure or analyze a dietary ingredient in order to determine whether a supplement in fact contains that dietary ingredient, it is reasonable for a proposed rule on CGMPs to include provisions related to identity, purity, quality, strength, and composition of a dietary ingredient or a dietary supplement. Moreover, it is reasonable to propose a requirement that records of complaints be kept and investigations be done, as necessary, so that the manufacturer and FDA can be aware of any potential problems relating to a particular dietary ingredient and these CGMPs, and so that a manufacturer can take appropriate action when necessary. The proposed CGMPs would reflect the act's regulatory scheme generally and, more specifically, DSHEA's provisions that contemplate consistent, controlled manufacture of dietary supplements (see sections 402(f) and 403(q)(5)(F) and (s) of the act). We tentatively conclude that, therefore, section 402(g)(2) of the act gives us the authority to develop dietary supplement

CGMPs that are not identical to our food CGMPs and that are appropriately tailored to the manufacturing, packaging, and holding of dietary ingredients and dietary supplements.

Sections 701(a) and 704 of the act also give us authority to establish regulations related to CGMPs for dietary ingredients and dietary supplements. Under section 701(a) of the act, we have the authority to issue regulations for the efficient enforcement of the act, and such regulations have been held to have the force and effect of law (see National Nutritional Foods Ass'n v. Weinberger, 512 F.2d 688, 697-98 (2d Cir. 1975)). Section 704 of the act gives us the authority to inspect factories, warehouses, and other establishments in which foods, including dietary ingredients and dietary supplements, are manufactured, processed, packed, or held and to inspect their facilities, equipment, finished and unfinished materials, containers, and labeling.

In addition to having the authority to establish broad regulations for manufacturing, packaging, and holding dietary ingredients and dietary supplements, we also have the authority to require recordkeeping as part of these regulations. Two questions that we considered in deciding whether to propose requirements for recordkeeping included whether the statutory scheme as a whole justified the proposed regulation and whether the proposed recordkeeping requirements would be limited, would

clearly assist in the efficient enforcement of the act, and would not create an unreasonable recordkeeping burden. In the other relevant sections of this document, we explain in more detail the recordkeeping provisions that we believe are limited to what are necessary for the efficient enforcement of the act, and because the requests are limited, would therefore not create an unreasonable recordkeeping burden.

For this proposed CGMP rule for dietary ingredients and dietary supplements, recordkeeping is necessary to provide the type of documentation that would demonstrate that dietary ingredients and dietary supplements are manufactured, packaged, and held under the conditions that would be required under the proposed CGMP regulations. Further, FDA is using its authority under sections 801 and 701(a) of the act in proposing recordkeeping requirements for dietary ingredients and dietary supplements that may not be marketed or sold in the United States and that are exported under section 801(e) of the act.

In addition to having the authority under the act to require recordkeeping, we also have authority to require access to the records. Because the practices set forth in the proposed CGMP rule are necessary to providing consumers with dietary supplements that are not adulterated, access to records that demonstrate that firms follow CGMPs is essential to confirming systematic compliance with CGMPs. We also have the authority to

copy the records when necessary. We may consider it necessary to copy records when, for example, our investigator may need assistance in reviewing a certain record from relevant experts in headquarters. If we were unable to copy the records, we would have to rely solely on our inspector's notes and reports when drawing conclusions. A failure to have a required record would mean that a food is adulterated under section 402(g) of the act.

Recordkeeping will not only help the agency to determine whether dietary ingredients or dietary supplements were manufactured, packaged, and held consistent with CGMP regulations, but also will provide a public health benefit to consumers. When manufacturers keep records, for example, of lot or batch numbers, the records facilitate a manufacturer's recall of suspect products in case a recall becomes necessary. This benefits consumers because the manufacturer can recall its products that may be adulterated or misbranded more quickly.

B. Issues From the ANPRM

As stated previously, in addition to inviting comment on the industry-drafted CGMP outline, we asked nine questions in the ANPRM on CGMP issues for dietary supplements that the industry outline did not address. In this section, we summarize each question and the principal comments we received, and we respond to the comments. We address other significant comments about the

ANPRM, other than the nine questions we asked, elsewhere in this document.

The nine questions in the ANPRM, comments, and our responses are as follows:

Question 1. Is there a need to develop specific defect action levels (DALs) for dietary ingredients?

The ANPRM stated that the use of a botanical in a dietary supplement may result in a much greater exposure to the botanical ingredient for consumers because the dietary supplement will be consumed in greater amounts than if the ingredient was in a food as a spice or flavoring agent.

Several comments stated that establishing DALs for dietary ingredients that are different than DALs for food is not necessary. The comments disagreed with our statement that dietary ingredients in dietary supplements and conventional foods are consumed in different quantities. For example, the comments stated that generally botanical ingredients are present in dietary supplements in approximately the same amounts normally consumed in conventional foods.

Other comments generally opposed applying the current DALs for foods to dietary ingredients and instead supported the development of DALs for dietary ingredients, especially for botanicals and herbals. Many comments recommended that we

cooperate with industry, outside the rulemaking process, to develop DALs for dietary ingredients.

We disagree with the comments that state that establishing DALs for dietary ingredients that are different than DALs for food is not necessary because an ingredient in food and in a dietary supplement would be consumed in the same amounts. The comment did not provide evidence or examples to support the comment. Some food ingredients for which DALs have been established also are dietary ingredients used in dietary supplements. For example, a DAL has been established for whole ginger used in a conventional food. Ginger is also a dietary ingredient used in dietary supplements. We have found dietary supplements that recommend a daily intake of ginger of 4,815 mg, 1,260 mg, and 2,200 mg (Ref. 38). One teaspoon of raw ginger root is equal to 2,000 mg (2 grams (g)) and one teaspoon of ground ginger is equal to 1,800 mg of ginger (1.8 g) (Ref. 39). A recipe for gingersnaps yielding 18 cookies specifies 1 teaspoon ginger (Ref. 40). Thus, ginger would be consumed in greater amounts as a dietary supplement than as an ingredient in a conventional food. However, we have tentatively concluded that we do not have sufficient information to determine whether a DAL for a dietary ingredient should be established at a different level than what has been established for the same ingredient used in conventional food.

DALs are established for a food ingredient on a per weight basis. The DALs for whole ginger for "insect filth and/or mold" is an "average of 3 percent or more pieces by weight are insect-infected and/or moldy" and for "mammalian excreta" is an "average of 3 mg or more of mammalian excreta per pound" (Ref. 41). Because the DAL is established by weight of the whole ginger, the DAL for ginger would apply whether it is used as an ingredient in a conventional food or a dietary ingredient in a dietary supplement. Therefore, if we have established a DAL in the industry compliance document for a conventional food ingredient, that DAL also would apply to that ingredient when used as a dietary ingredient in a dietary supplement until such time that we would establish a different DAL for its use as a dietary ingredient (Ref. 41). However, we do not have many dietary ingredients that are included in the DAL compliance guide. We agree that DALs may be needed for some dietary ingredients, especially ingredients like botanicals that are subject to the same type of defects (such as mold and insect parts) as other food for which DALs have been established. We base DALs on scientific information such as literature surveys, scientific market surveys, and laboratory analyses and also on information gained through physical plant inspections. If and when we determine that we have sufficient information to develop DALs for dietary ingredients, we will consider whether to do so.

Question 2. We requested comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements.

The ANPRM explained that the misidentification of dietary ingredients, particularly plant materials, used in dietary supplements may present a significant public health and economic concern. The ANPRM also noted that the analytical methodology available for identifying many dietary ingredients is limited. We invited comments on the technical and scientific feasibility of identifying different types of dietary ingredients. We also solicited information on what constitutes "adequate testing" for identity of different types of dietary ingredients, and, in the absence of testing, what types of practices would be effective alternatives to testing to ensure the identity of different types of dietary ingredients.

Comments generally supported requiring tests of some kind to positively identify dietary ingredients and to verify dietary ingredient identity. The comments put forth different reasons, which ranged from ensuring public safety to preventing economic adulteration. Some comments suggested that suppliers should be responsible for identifying the dietary ingredients they supply to manufacturers and that manufacturers should be responsible for only verifying the identity of the finished product. Other

comments stated that the manufacturer should be responsible for identification and should not rely on a supplier's certification.

Some comments raised issues relating to the actual identity tests that should be recommended or required and discussed analytical method selection and method options, use of and availability of official validated analytical methods, and certification of testing facilities that conduct identity tests on natural products. Some comments suggested that identity test method options should include organoleptic and microscopic methods and chemical analytical methods. The comments noted that selecting the appropriate method is dependent on the type and form of the ingredient. Other comments said that manufacturers should be responsible for selecting the appropriate method to confirm ingredient identity. Most comments recommended that we provide guidance to industry in defining what comprises adequate testing for different types of ingredients, but did not support regulations prescribing the test method or methods for specific ingredients.

Comments generally supported the use of a standard compendial method, such as those published by the USP or AOAC International. Where no published method exists, the comments suggested that manufacturers should be responsible for developing adequate and effective identification testing procedures, requirements, or practices to ensure the identity of the dietary

ingredients they use. One comment from a vitamin manufacturer noted that most of its products have recognized and established identity tests as part of their compendial status. Other comments from botanical dietary supplement manufacturers noted that their current methods for identifying plant material are adequate, but that they will, over time, be enhanced by the availability of more widely recognized methods and techniques as a result of current work in this field. The comments noted that test methods that are presently available and used for identifying botanicals are not officially validated. If an officially validated method is not available for a dietary ingredient, several comments suggested working towards AOAC International validation and, in the interim, instituting peer review of less formal test methods. Other comments noted that the dietary supplement industry has begun an effort to develop validated test methods for several botanical ingredients. One comment suggested that it is important to develop methods that are subject to peer review and to institute a certification program for testing facilities because the analysis of natural products requires specialized training in natural product chemistry. The comment did not indicate who (e.g., FDA or another organization) should develop a certification program.

Some comments only addressed identity testing of unprocessed botanicals. These comments said that for unprocessed botanicals

in whole or in part (e.g., flowers, roots, leaves, etc.), organoleptic techniques are sufficient provided that accurate records are maintained and that the manufacturing process provides a paper trail of positive identification. One comment suggested that a "voucher specimen" (a sample of the plant material) from the supplier along with a certificate of botanical identity would be an adequate record. The certificate of botanical identity would follow the material through the manufacturing process, thus creating a paper trail. The voucher specimen would be held for a specific period of time or, if necessary, serve as a permanent record.

Dietary ingredient identification is an important part of CGMPs. We agree with the comments that identity testing requirements are needed but that no single approach or test method may be appropriate for every dietary ingredient. For example, microscopic or organoleptic tests might be appropriate for herbs or plant parts (because you can see, taste, or smell them), but not appropriate for amino acids (which cannot be identified by the naked eye or identified by using your senses). A microscopic test might be appropriate for herbs that still have their leaves or other distinguishing marks or characteristics, but not for ground-up herbs. Thus, we agree with the comments stating that the key principle in dietary ingredient identification testing is to establish an appropriate procedure

that will identify, with certainty, the dietary ingredients used in making a dietary supplement. We agree that a guidance document on ingredient identity testing may be useful, and we will consider future development of ingredient identity testing guidance documents.

Manufacturers should be responsible for identifying the ingredients that they use in their products and, in addition, for verifying that the dietary ingredients or dietary supplements they make contain the identity, purity, quality, strength, and composition that the manufacturer intends the product to have. As discussed previously in this document, we have found serious adverse events to be related to dietary ingredient misidentification. The manufacturer must conduct identity tests to ensure that they used the correct ingredient to prevent potential serious adverse events. We discuss identity testing for dietary ingredients and dietary supplements later in this document.

We agree with the comments that certification of testing facilities could be an important step in ensuring analytical quality. However, certification of testing facilities is outside the scope of this rule.

Question 3. FDA requested comments on standards that should be met in certifying that a dietary ingredient or dietary supplement is not contaminated with filth; that it is free

of harmful contaminants, pesticide residues, or other impurities; that it is microbiologically safe; and that it meets specified quality and identity standards.

The ANPRM noted that, under § 110.80, a food manufacturer may accept a supplier's certification that its products do not contain microorganisms, filth, or other foreign material that would adulterate the product instead of testing or evaluating the supplier's products itself. As a result, we asked for comments on whether a certification will provide assurance that dietary ingredients are not contaminated or whether specific testing requirements are necessary.

Comments generally supported relying on a supplier's certification that a dietary ingredient is what it purports to be and is not contaminated. The comments stated that reliance on the supplier's certification should be an alternative to testing raw materials to detect microorganisms, filth, or foreign material so long as the reliability of the supplier's certification is confirmed. Most comments stated that manufacturers are responsible for determining, on a case-by-case basis, whether a supplier's certification provides adequate assurance that a dietary ingredient is what it purports to be and is not adulterated. Some comments based their support for relying on a supplier's certification on § 110.80(a)(2) through (a)(4); these provisions allow food manufacturers to rely on a

supplier's guarantee or certification that raw materials or other ingredients do not contain levels of microorganisms or toxins that may produce illness or are otherwise contaminated. The comments suggested various means for determining the reliability of a supplier's certification, including independent analysis, in-house testing, and review of protocols.

Other comments stated that, because the CGMP regulations in part 110 permit reliance on a supplier's certification and because section 402(g)(2) of the act specifies that the CGMP regulations for dietary supplements should be modeled after the CGMP regulations for food, a supplier's certification for dietary supplements must be acceptable.

We have considered the comments on whether a supplier's certification could provide adequate assurance that a dietary ingredient is what it purports to be and is not adulterated. We disagree that manufacturers may rely on such certifications to determine that an ingredient is not contaminated, for example, with filth or microorganisms. Using a supplier certification, guarantee, or certification in lieu of performing testing on each shipment lot of components, dietary ingredients, or dietary supplements is not appropriate because a supplier's certification or guarantee would not necessarily ensure that the identity, purity, quality, strength, or composition of a component, dietary ingredient or dietary supplement is met. We discuss testing

requirements and why we believe that the use of supplier's guarantee or certification is not sufficient in lieu of a manufacturer's own testing in more detail later in this document.

Question 4. We asked for comments on whether a CGMP rule should require manufacturers to establish procedures to document, on a continuing or daily basis, that they followed preestablished procedures for making dietary supplements.

The ANPRM noted that the food CGMP regulations under part 110 do not require manufacturers to document that they are following established procedures prescribed for manufacturing a food. However, the ANPRM also noted that section 402(g) of the act does not preclude us from adopting CGMP requirements for dietary ingredients and dietary supplements that have no counterpart in part 110 if we have an appropriate basis for doing so.

Most comments generally supported requiring manufacturers to develop and follow written procedures and noted that the industry outline in the ANPRM would require written procedures for many processes and functions. Some comments noted that written procedures and day-to-day records documenting that the procedures were followed will ensure that products are safely and properly manufactured on a day-to-day basis and that this can be confirmed by periodic independent internal audits. One comment stated that the manufacturer should be responsible for ensuring, through employee training, self-audit programs, and batch records, that

quality control and other procedures prescribed for the manufacture of a dietary supplement are properly and diligently executed. Other comments stated that it is good business practice to ensure product quality through periodic review of records and quality control audits and that failure to establish procedures will result in product recalls, potential injury, and litigation for damages for defective goods.

Some comments objected to any requirement for written procedures or documentation that the procedures were followed. The comments stated that section 402(g)(2) of the act states that dietary supplement CGMPs must be modeled after the food CGMP regulations and the food CGMP regulations do not require written procedures or documentation that procedures were followed.

We agree with those comments that support the development and use of written procedures by manufacturers and are considering whether we should require written procedures in a final rule. We are proposing requirements for documenting certain operations and processes while not requiring written procedures to remove underlying costs for establishing and updating such written procedures while preserving the records necessary to permit trace back. When manufacturers develop and follow written procedures such procedures help to ensure that manufacturers produce a consistent dietary ingredient or dietary supplement that is of a predictable quality and that is not

adulterated. Following written procedures and dccumenting compliance with those procedures will ensure regular performance of a firm's established programs and procedures and will provide additional assurance of effective communication of appropriate information from the firm management to the line personnel. We invite comment on whether written procedures should be required in a final rule, and whether there are other procedures, that we should include in a final rule. We discuss written procedures for various stages of manufacturing, packaging, labeling, holding, and for handling consumer complaints later in this document.

We disagree, however, that records are not necessary to show that certain operations and processes are being performed. Records document that quality control operations and processes such as calibrating instruments and controls; manufacturing a dietary ingredient or dietary supplement batch; and handling consumer complaints were performed. We further discuss the basis for the proposed recordkeeping requirement for certain operations and processes later in this document. We believe that section 402(g) of the act allows us to require written procedures and documentation that the procedures were followed. As explained previously, such records may be necessary for ensuring that dietary ingredients and dietary supplements are manufactured, packaged, and held consistent with these regulations. Moreover,

we believe that the fact that the food CGMPs in part 110 do not have recordkeeping requirements does not preclude us from proposing recordkeeping requirements in this proposed rule, although we seek further comment on the issue.

Question 5. We invited comment on whether dietary supplement CGMP regulations should require that firms have competent medical authorities evaluate reports of injuries or illnesses and to determine if followup action is necessary to protect the public health.

The ANPRM explained that many dietary supplements contain pharmacologically active substances, which distinguish dietary supplements from many foods, and some dietary supplements may contain potential allergens. Because the characteristics may result in adverse events in certain consumers, we asked whether we should consider requiring firms to take certain actions with respect to reviewing AERs. We also sought comments on whether a CGMP rule should require firms to establish procedures for determining whether a reported injury constitutes a serious problem, and what actions are to be taken when serious problems are identified.

Comments generally opposed requiring manufacturers to establish a procedure for evaluation and followup of reports of illness and injuries. Comments also opposed requiring that a competent medical authority evaluate all reports of illness or

injuries to determine if followup action is necessary to protect the public health. Some comments, opposing requiring written procedures and evaluation, suggested alternatives to requirements, such as using the Centers for Disease Control and Prevention, poison control centers, FDA's MedWatch program, and consumer complaint files to monitor and record injuries and illnesses attributed to marketed products.

In contrast, several comments supported a requirement for written procedures or medical evaluation of serious adverse events. Some comments stated that an evaluation procedure is necessary and that manufacturers are and should be responsible for establishing procedures to respond appropriately to reports of serious illness and injury that may have resulted from using a dietary supplement. Other comments stated that medical evaluations are not necessary because manufacturers should be using appropriate internal quality control procedures within their quality control units or elsewhere to identify the cause of adverse events and respond appropriately.

We agree with those comments stating that manufacturers are and should be responsible for evaluating consumer complaints. Manufacturers have an obligation to ensure that the dietary supplements that they put on the market are not adulterated or misbranded. Consumer complaints about a dietary supplement might indicate a CGMP-related problem associated with a dietary

supplement. For example, a consumer complaint might identify a previously unknown manufacturing deviation that caused a batch of dietary supplements to be adulterated. Thus, a procedure for reviewing and investigating consumer complaints is recommended. Records of consumer complaints related to CGMPs, and the review and investigation of such records, are necessary and we discuss such a record requirement later in this document. In that discussion, we address what we mean by a consumer complaint and we address the comments on the type of evaluation that would be necessary for consumer complaints and whether the comments' suggested alternatives to written procedures and medical evaluations are sufficient to identify potential concerns.

Some comments objected to written procedures and medical evaluation arguing that such requirements go beyond the CGMP regulations for food and, therefore, would be contrary to section 402(g)(2) of the act. Other comments claimed that written procedures would present unwarranted potential criminal liability, that there are many unsubstantiated injuries and illness inherent in the food industry, and that dietary supplement safety problems are rare. These comments also stated that a costly and burdensome safety surveillance system is not warranted for these products, that the term "serious adverse event" is ambiguous, and that most manufacturers lack trained medical personnel to serve this function.

Because we have found dietary supplement problems that could have been prevented by CGMPs and that resulted in product recalls, we find that manufacturers must be able to identify these types of problems with their products. It is a manufacturer's responsibility to do so. We disagree with those comments stating that we do not have legal authority to require a manufacturer to evaluate consumer complaints as we propose to define that term in this proposed rule.

We also disagree that written procedures would present unwarranted potential criminal liability. Persons subject to regulation under the act and its implementing regulations may face civil or criminal action if they fail to comply with the act or our regulations (see, e.g., sections 301, 302, and 303 (21 U.S.C. 331, 332, and 333) of the act). The fact that such an outcome is possible under the statutory scheme does not mean that a provision that would require written procedures and evaluation of consumer complaints is "unwarranted." If we were to accept such a claim, then we would find it difficult to issue any regulation to implement the act, and that result would conflict with our obligation to protect the public health. Therefore, we reject the comments' argument regarding potential criminal liability and its effect on rulemaking.

We also disagree with the claim that there is no basis for requiring an evaluation of adverse events because there are many

unsubstantiated reports of injuries or illness and because dietary supplement safety problems are rare. In the past, voluntary reports of injury or illness have identified adulterated dietary supplements. Consumer complaint reports associated with the use of marketed dietary supplements, such as D. lanata contaminated plantain, identified the need for further investigation and led to recalls or warnings to protect the public health (Ref. 6). Evaluation of consumer complaint reports can reveal patterns of adverse events that assist us and manufacturers in identifying the need for further investigation to determine what public health actions are needed.

For example, assume that, after you investigate an AER, you find that the product contained an ingredient that should not have been used and that the ingredient caused the adverse event. The fact that the wrong ingredient appeared in your product would indicate that some type of problem occurred in your manufacturing process of that product. Once you identify the ingredient as the cause of the problem, you would be able to take steps to remove any such product from the market and prevent the problem from recurring, helping to ensure product quality and purity, and restore consumer confidence that your products contain the correct ingredients. In short, investigations of consumer complaints benefit both manufacturers and consumers and these benefits will exist regardless of whether there are many or few

injuries or illnesses believed to be associated with your product.

Question 6. We invited comment on whether a CGMP regulation for dietary supplements should require manufacturers to establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients. We asked whether such an evaluation is necessary, and, if so, what elements need to be included in such an evaluation and their relative importance (e.g., the presence and potency of pharmacologically active substances, the presence of different microorganisms, the presence of different contaminants and impurities). We also asked whether we should require that these evaluations be documented in a firm's records, and, if so, what type of records would be adequate to document that such an evaluation had occurred.

In general, the comments opposed requiring manufacturers to establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients. Most comments claimed that such procedures are unnecessary because dietary ingredients have a history of safe use in food and that DSHEA is based on this history of prior use in food. Other comments argued that, because DSHEA is based on a history of prior use of existing dietary supplements and established a notification procedure for new dietary ingredients, a requirement

concerning potential safety concerns for dietary ingredients would be beyond the scope of this rulemaking.

Several comments noted that for those dietary ingredients that do not have a history of safe use in food and are considered "new dietary ingredients," as defined in section 413(c) of the act, DSHEA established procedures for evaluating safety concerns. Section 413(a)(2) of the act requires a manufacturer to submit a "new dietary ingredient" notification to FDA 75 days before introducing or delivering a dietary supplement containing a new dietary ingredient into interstate commerce. The notification must provide the basis upon which the petitioner has concluded that the dietary supplement containing the new dietary ingredient is reasonably expected to be safe. Therefore, the comments argued that procedures to identify, evaluate, and respond to potential safety concerns are not necessary in a CGMP rule.

Other comments stated that FDA should not require procedures to identify, evaluate, and consider potential safety concerns with dietary ingredients because manufacturers already have an essential and critical responsibility to substantiate the safety of the dietary ingredients they use in manufacturing a product. The comments suggested that FDA does not need to require written procedures because manufacturers must consult the generally known and generally available scientific literature to determine that a dietary ingredient is safe. Some comments suggested that,

instead of FDA requiring safety evaluations, a third-party could evaluate safety concerns. Several comments suggested that manufacturers who use dietary ingredients that have little history of use in food in the United States should retain documentation concerning the dietary ingredient's safety. One comment suggested that we issue a guidance document to identify the types of acceptable "history of use" standards for dietary ingredients having little history of use in food in the United States and to describe the documentation that would be needed regarding a dietary ingredient's safety.

Although the comments focused on the safety of using particular dietary ingredients, the safety concerns described in question 6 actually consist of two concepts: (1) Is the product formulated using safe dietary ingredients; and (2) is the product manufactured, packaged, and held in a manner that would not adulterate or misbrand the product? The proposed rule focuses on safety concerns related to the latter concept. Specifically, the proposed rule focuses on the steps and processes used in the manufacturing, packaging, and holding of the product to ensure, for example, that the product has the identity, purity, quality, strength, and composition claimed and does not become adulterated or misbranded. The agency notes that no comments appeared to argue that safety issues relating to potential contamination or adulteration related to manufacturing processes are outside

CGMPs. As the comments recognize, manufacturers have an essential and critical responsibility to substantiate the safety of the dietary ingredients they use in manufacturing a product.

Section 402(g) of the act is not the only provision relevant to whether a dietary ingredient or dietary supplement may be deemed to be adulterated. Section 402(f)(1) of the act, in part, declares a dietary supplement to be adulterated if it:

- Presents a significant or unreasonable risk of illness or injury under conditions of use described in the labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use;
- Is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that the dietary ingredient does not present a significant or unreasonable risk of illness or injury; or
- Is or contains a dietary ingredient that renders it adulterated under section 402(a)(1) of the act under the conditions of use recommended or suggested in the labeling. (Section 402(a)(1) of the act declares a food to be adulterated if it contains substances that are poisonous or deleterious substance that may render it injurious to health.)

Additionally, section 301(a) of the act prohibits the introduction of adulterated food into interstate commerce.

So, for a dietary ingredient or dietary supplement manufacturer to comply with sections 301(a) and 402(f)(1) of the act, it must take steps regarding potential safety concerns before it markets the product. Otherwise, if the manufacturer had no obligation to evaluate possible safety concerns before marketing a product, sections 301(a) and 402(f)(1) of the act would not make sense and the manufacturer would be acting contrary to the basic congressional intent behind DSHEA, which was to ensure that safe dietary supplements are available to consumers. For example, assume that a manufacturer wanted to market a new dietary ingredient but lacked evidence to show that it is safe. Under section 402(f)(1)(B) of the act, the manufacturer must have adequate information to provide reasonable assurance of the dietary ingredient's safety before it markets the dietary ingredient; otherwise, the dietary ingredient is adulterated under section 402(f)(1)(B) of the act, and section 301(a) of the act would prohibit its sale in interstate commerce. Thus, the manufacturer has a statutory obligation to examine safety concerns relating to the dietary ingredients it uses before it markets the product.

The proposed CGMP rule focuses on ensuring that the manufacturer knows what it is putting in its product and is

manufacturing, packaging, and holding the product in a manner that will not adulterate or misbrand the product. For example, assume that you use a particular herb as your dietary ingredient. However, there are different species of that herb. Some species are poisonous; others are not. Additionally, there are variations within the same species of herb depending on where the herbs were grown. Some variants may contain higher levels of a particular dietary ingredient or marker compound than other variants. So, how do you know whether you have the right herb (nonpoisonous species of herb intended for use) and whether it meets your specifications? CGMPs would require that you check the identity of the herbs you receive; by doing so, you would be able to tell whether you have the correct herbs, whether your herbs are poisonous, or whether they meet your specifications. In this example, the potential safety concerns involve the dietary ingredient itself rather than any issue concerning contamination which would adulterate or may lead to adulteration of the dietary ingredient, and thus, the dietary supplement which contains the dietary ingredient.

As for the comments' arguments concerning a dietary ingredient's history of use, we do not need to address history of use as part of this CGMP proposal. CGMPs focus on how a product is made under current manufacturing processes. A dietary ingredient's history of use does not provide any assurance that a

particular product has the identity, purity, quality, strength, and composition that it purports to have. Further, history of use does not necessarily provide any assurance that a particular product would not pose a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or under ordinary conditions of use.

As for those comments discussing whether manufacturers or other parties should evaluate potential safety concerns, the proposed rule would require a manufacturer to evaluate a consumer complaint to determine whether the complaint relates to good manufacturing practices. Such an evaluation would include possible hazards to health resulting from the manufacturing, packaging, or holding of a product. Nevertheless, you should note that, insofar as compliance with the act and any CGMP regulations are concerned, persons who market dietary ingredients and dietary supplements always remain responsible for their products. If the manufacturer markets the product, it would have to meet all proposed CGMP requirements, if the agency finalizes the rule as proposed. If another person buys a product (such as bulk dietary ingredients) from a manufacturer and distributes the product under its own name, that person must meet all applicable CGMP requirements.

Question 7. We invited comment on whether specific controls are necessary for computer-controlled or assisted operations

and how best to ensure that the software programs and equipment used to direct and monitor the manufacturing process are properly designed, tested, validated, and monitored.

Comments generally supported specific controls for computer-controlled or computer-assisted operations. One comment suggested requiring manufacturers to confirm, by adequate and documented testing, that their computer software programs perform their intended functions when computers are used as part of an automated production system having a significant and direct impact on product safety. Another comment suggested requiring that software programs and equipment used to direct and monitor manufacturing processes are properly designed, tested, evaluated, and monitored. The comment added that, if we consider imposing specific requirements on how firms document the adequacy of their computer-controlled or assisted operations, we should address those recommendations through a guidance document instead of issuing regulations.

We agree that computer-controlled or computer-assisted operations need to be properly designed, tested, evaluated, and monitored to ensure that the computers do what they are supposed to do. Manufacturers should confirm, by adequate and documented testing, that their computer software programs perform their intended functions because computer use as part of an automated

production system has a significant and direct impact on product safety. Computers are an important controlling piece of equipment in the manufacture of dietary supplements because they often direct and control key steps or processes in the manufacture of dietary supplements. If computers do not operate correctly, the dietary supplements manufactured using those computers may be adulterated.

Several comments supported requirements for specific controls, but opposed using validation-of-operation mandates like those in the CGMP regulations for drugs. One comment suggested that we regulate computer-controlled and computer-assisted operations for dietary supplements in the same way that we regulate such operations in the pharmaceutical industry, but only where an operation is directly related to the product's concentration or purity. One comment suggested that we consider adopting the computer-controlled and computer-assisted procedures specified in the proposed infant formula CGMP.

We propose general requirements to ensure that equipment is suitable for its intended use. However, we seek comment, in the proposed rule, about whether we should include requirements, written procedures, and records for equipment verification and re-verification. We request comment on what verification manufacturers should be using in their computer-controlled or computer-assisted operations to ensure that a dietary ingredient

or a dietary supplement that is produced is not adulterated during manufacturing. In addition, we request comment on whether we should issue guidance documents on verification procedures for use with computer-controlled or computer-assisted operations. Guidance documents generally represent FDA's advice or current thinking on a particular matter and are not binding on any person. In contrast, regulations create enforceable requirements that apply to all persons engaged in the same action or who make the same product.

As discussed in greater detail later in this document, certain processes are necessary to ensure that computer-controlled or computer-assisted equipment functions properly. This is because of the important role of such equipment in manufacturing. For example, if computer-controlled or computer-assisted equipment is used to control components, inprocess materials, and rejected materials unsuitable for use, the operation must function as expected to ensure that components suitable for use in manufacturing dietary ingredients and dietary supplements are not mixed up with components held under quarantine such as those components that have been rejected as unsuitable for use. If computer-controlled or computer-assisted operations are used for the addition and mixing of components, they must function properly to ensure that the correct components are added and appropriately mixed to avoid producing a dietary

ingredient or dietary supplement that is adulterated. Computer-controlled or computer-assisted operations are not perfect; computers are subject to malfunctions and "bugs" (errors) in the software they use. Problems with data entered into the computer may produce unreliable results. For these reasons, specific controls for computer-controlled or computer-assisted operations are necessary to prevent the manufacture of an adulterated dietary ingredient or dietary supplement.

A few comments stated that no specific requirements for computer-controlled or computer-assisted operations are needed because computer hardware and software are simply specialized plant equipment so that no special regulations are needed.

We agree that computers are specialized pieces of plant equipment and, therefore, should be subject to additional requirements beyond those which would apply to plant equipment. Computers are specialized pieces of equipment because they are subject to malfunctions and "bugs" (errors) in the software, they are reliant upon data entered into a computer, and they may be used to perform important roles such as component or dietary ingredient identification, measuring components and dietary ingredients, and quarantining materials. Consequently, proposed § 111.30 would establish requirements for automatic, mechanical, or electronic equipment. The proposed requirements would cover, among other things, automatic equipment design, and routine

calibration, inspection, and checks to ensure proper performance. As stated previously, we are seeking comment on whether we should include requirements for verification and re-verification of automatic, mechanical, or electronic equipment and processes and whether we should include requirements for computerized systems that are separate from requirements for other mechanical or automatic equipment. We discuss proposed § 111.30 in greater detail later in this document.

Question 8. We asked for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be more effectively addressed by a regulation based on the principles of Hazard Analysis and Critical Control Point (HACCP), rather than the system outlined in the industry submission.

In the ANPRM, we noted that, because of the wide variety of dietary ingredients and dietary supplements and because of the heterogenous composition of the dietary supplement industry, CGMPs based on HACCP principles may provide a more flexible and less burdensome regulatory framework for manufacturers and distributors than the approach set out in the industry submission.

Most comments opposed basing a CGMP regulation for dietary ingredients and dietary supplements on HACCP principles. Most

comments supported applying traditional CGMP requirements on manufacturing, packaging, and holding to dietary ingredients and dietary supplements. In general, the comments that opposed requiring HACCP for dietary ingredients and dietary supplements asserted that: (1) A HACCP program would not be appropriate because HACCP focuses on microbial contamination of products that provide a favorable environment for growth of microbes that may be present, and these hazards are not a major concern for dietary supplements; (2) CGMPs are the best means of assuring the safety, quality, and composition of dietary ingredients and dietary supplements; (3) HACCP is not required for the food industry as a whole; and (4) HACCP would provide minimal incremental value at significant additional costs.

Other comments opposed mandatory HACCP regulations for dietary ingredients and dietary supplements, but said manufacturers could implement voluntarily HACCP instead. One comment, which supported voluntary implementation of HACCP, wanted manufacturers to be exempt from having to disclose HACCP records to any Federal agency.

HACCP principles can be applied to a broad range of manufacturing practices and HACCP principles are not solely focused on microbial contamination, but instead, are intended to identify and appropriately control steps in manufacturing where any type of adulteration can occur. Nevertheless, after

considering the comments, we have decided to propose a CGMP approach fcr dietary ingredients and dietary supplements. We believe that CGMPs would establish a system of controls that, given the variations in size, technological sophistication, and regulatory experience among dietary ingredient and dietary supplement firms, would create a strong regulatory foundation throughout the industry.

You may voluntarily choose to implement a HACCP plan that meets the requirements of the National Advisory Committee on Microbiological Criteria for Foods, however, proposed part 111 would still apply to you (Ref. 42). Any HACCP plans that also are intended to meet the records requirements under proposed part 111 would be treated as records under this proposal.

Question 9. We invited comment on whether broad CGMP regulations will be adequate, or whether it will be necessary to address the operations of particular segments of the dietary supplement industry.

Most comments supported broad CGMP regulations covering all segments of the dietary supplement industry instead of specific regulations tailored to distinct segments of the industry. One comment stated that the differences between distinct segments of the dietary supplement industry, such as manufacturers of raw materials or distributors of finished products, are no more pronounced than similar segments in the food industry. Another

comment stated that having numerous CGMPs could subject raw materials and dietary ingredients to multiple CGMPs, thus making manufacturing operations more complex. This comment also questioned whether issuing multiple regulations is necessary or economically justified in an era of limited corporate and government regulatory resources. Other comments emphasized the importance of ensuring that all dietary supplement manufacturers (i.e., both small and large manufacturers, and foreign manufacturers planning to import dietary supplements into the United States) follow the same CGMP requirements.

In contrast, some comments supported drafting regulations for particular segments of the dietary supplement industry. One comment stated that certain stages of the manufacturing process, such as the distribution of raw dietary ingredients, should be more strictly and comprehensively regulated than other stages because potential hazards are more prevalent during these manufacturing stages. The comment stated that conversely, the holding, distribution, and sale of a finished dietary supplement may require less comprehensive regulations because they are subject to fewer potential hazards. Other comments supported different levels of safety testing for different types of dietary supplement products. For example, some comments said that products such as melatonin and dehydroepiandrosterone resemble drugs, so we should require safety testing in animals and humans

and impose druglike CGMP requirements for manufacturing. Another comment stated that less stringent CGMPs would be appropriate for herbal dietary supplements because they have long histories of food use and safety.

We agree that some manufacturing operations are subject to greater hazards than others, and have drafted the proposed rule accordingly. For example, there are microbial hazards associated with raw botanicals. To address these hazards, the proposal would require that you perform tests on the botanicals. On the other hand, there are fewer hazards associated with holding and distributing finished dietary supplements, so the proposal would impose less comprehensive requirements for holding and distributing operations.

We are persuaded by the comments that support a broad CGMP regulation as preferable to multiple regulations focused on particular segments of the industry. We agree with the comments that multiple regulations might be confusing and burdensome, especially to firms that manufacture products that fall into multiple categories. For instance, it would be easier for regulated firms and for us if firms were required to adhere to one set of CGMP requirements rather than follow, for example, one set of CGMP requirements for vitamins and a different set of CGMP requirements for minerals.

We also recognize, though, that there may be some reasons to treat different types of dietary ingredients or dietary supplements differently in specific instances. For example, it may be appropriate to require one type of test for confirming the identity of amino acids and another type of test for confirming the identity of herbals. However, for the reasons discussed previously, we are proposing to establish one set of broad CGMP regulations for all types of products. Because we recognize that one set of specific requirements may not be appropriate for all types of dietary ingredients and dietary supplements, we have proposed regulations that allow manufacturers to develop practices to meet CGMP requirements. Depending on our experience with this proposed rule, we will consider whether we need to reevaluate our decision to establish one set of requirements for all dietary ingredients and dietary supplements.

We agree with the comments that the proposed rule should not make any distinction between dietary ingredients or dietary supplements made in the United States and those made in a foreign country. The proposed rule would require that foreign firms that want to export dietary ingredients and dietary supplements to the United States manufacture, package, and hold dietary ingredients and dietary supplements consistent with proposed part 111. Moreover, under this proposed rule, if a U.S. firm contracts with a foreign firm to package dietary supplements for sale in the

United States, the imported product would have to comply with the requirements in proposed part 111. In addition, the U.S. firm would be required to meet all applicable CGMP regulations under this proposed CGMP rule related to those activities in which it engages under the proposed rule. We invite comment on how best to ensure that dietary ingredients and dietary supplements exported to the United States have been manufactured, packaged, and held consistent with part 111.

This proposal does not include requirements for safety testing in animals and humans for certain types of dietary ingredients and dietary supplements. As discussed in several parts of this preamble, you are responsible for ensuring that the dietary ingredients or dietary supplements that you make are safe prior to marketing such products. Although we are focusing on the manufacturing steps in actual production and distribution of dietary ingredients and dietary supplements, there may be the need for specific regulations related to the use of animal tissue. We invite comment on whether there is a need for such specific regulations.

III. Description of the Proposed Rule

This proposal will supercede what the agency said about the placement in Title 21 of the Code of Federal Regulations for any regulations resulting from the proposed rule for dietary supplements containing ephedrine alkaloids (62 FR 30678, June 4,

1997). That proposal included proposed revisions of part 111 and the table of contents for part 111 and we are now proposing those for 21 CFR part 112 (as explained below).

This proposal for dietary supplement CGMPs amends part 111 (21 CFR part 111), revising the heading from "Current Good Manufacturing Practice for Dietary Supplements" to "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements." Proposed part 111, with the heading "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements," includes only the CGMP for dietary supplements and the table of contents contains categorical CGMP practices in subparts A through H.

Further, we propose the heading and table of contents for part 112. Proposed part 112 has the heading "Restrictions for Substances Used in Dietary Supplements." The table of contents for proposed part 112 includes: Subpart A "General Provisions" [Reserved]; Subpart B "New Dietary Ingredients" [Reserved]; and Subpart C "Restricted Dietary Ingredients" [Reserved]. Proposed subpart C would include restrictions for substances used in dietary supplements, such as the proposed rule for dietary supplements containing ephedrine alkaloids, if finalized.

These proposed changes are made for ease of use and clarity. CGMP regulations will be found more easily if located in one

part, part 111, and clarity will be enhanced by using subparts to organize categorical CGMP practices. Similarly, restrictions for substances used in dietary supplements will be found more easily if located in one part, part 112, and clarity will be enhanced if the restrictions for substances used in dietary supplements are located in one subpart, subpart C.

The proposed part 111 consists of eight subparts. Several of the proposed provisions in the CGMP regulations for dietary ingredients and dietary supplements are similar to the CGMP regulations for food products at part 110. However, we edited the text in many cases to make the proposed rule easier to read and to understand consistent with plain language principles under the presidential memorandum of June 1, 1998 (Ref. 43). Some provisions are derived from the industry outline that we included in the ANPRM; others are derived from comments we received on the ANPRM or from our outreach efforts described previously. We also developed provisions based on our knowledge and expertise in the areas of dietary supplements, manufacturing, and contamination.

We tentatively decided to exclude certain CGMP requirements in part 110 for food products because they do not appear to be appropriate for dietary ingredients and dietary supplements. There are differences in the nature of the product (i.e., conventional food versus dietary ingredients or dietary supplements) and in the manufacturing practices used to produce

the product that require specific practices appropriate for dietary ingredients and dietary supplements. We invite comment on whether any provision from part 110 that we have not included should be included in this proposed CGMP for dietary ingredients and dietary supplements.

A. General Provisions (Proposed Subpart A)

Proposed subpart A contains five provisions that would provide basic information to the reader.

1. Who Is Subject to These Part III Regulations? (Proposed § 111.1)

Proposed § 111.1 entitled "Who is subject to these regulations?" describes the scope of the rule. Proposed § 111.1 states that you are subject to the requirements in part 111 if you manufacture, package, or hold a dietary ingredient or dietary supplement. As stated previously in this document, in our response to question 9 of the ANPRM, this proposed CGMP rule would apply to a wide variety of activities associated with the manufacture, packaging, and holding of dietary ingredients and dietary supplement products. These activities include labeling, testing, quality control, holding, and distribution. For example, if you contract with a manufacturer to perform an operation subject to proposed part 111, you will need to comply with those regulations directly applicable to the operation that you perform. For example, if you are a firm that has contracted

with a dietary supplement manufacturer to package a dietary supplement, you are responsible for complying with all the regulations, including recordkeeping, that would otherwise be required of a manufacturer who does its own onsite packaging. Further, if you are a manufacturer and you contract with a firm to perform a particular manufacturing step, you would remain responsible for ensuring that such step is done in a manner that complies with the requirements in proposed part 111. As in the previous example, a manufacturer who contracts with a firm to package a product is still responsible for the actions of its contractor for the packaging activities and must ensure that its contractor complies with the applicable CGMP regulations.

Proposed part 111 also would apply to foreign firms that manufacture, package, or hold dietary ingredients and dietary supplements that are imported or offered for import into the United States, unless imported for further processing and export under section 801(d)(3) of the act, to persons who distribute such imported dietary ingredients and dietary supplements, and to persons who export dietary ingredients and dietary supplements from the United States, unless exported in compliance with section 801(e).

One comment to the ANPRM, relating to the scope of the CGMPs, requested an exemption from the CGMP for "herbalist"

practitioners who individually manufacture dietary supplements for their clients.

We decline to exempt herbalist practitioners from the proposed rule. If an herbalist practitioner introduces or delivers for introduction into interstate commerce, a dietary ingredient or dietary supplement, that practitioner must use the same good manufacturing practices as other manufacturers to ensure that their clients receive dietary supplements that are not adulterated. The risks of adulteration are not eliminated just because the practitioner is an herbalist. Therefore, we decline to exempt "herbalist" practitioners who manufacture dietary ingredients and dietary supplements. Herbalist practitioners who introduce or deliver for introduction into interstate commerce, a dietary ingredient or dietary supplement, are manufacturers who must meet CGMPs.

2. What Are These Regulations Intended to Accomplish? (Proposed § 111.2)

Proposed § 111.2, entitled "What are these regulations intended to accomplish?" discusses the purpose of the CGMP regulations. The proposal states that the regulations establish the minimum CGMPs that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement. By using the phrase "to the extent," we mean that you must comply with the provisions that are applicable to you or

to the operations that you perform and that, depending on the type of operations you perform, some provisions may not apply to you. For example, some provisions discuss requirements for automatic, mechanical, and electronic equipment; if you do not use such equipment, you would not have to comply with those provisions.

Our primary purpose in proposing these regulations is to protect consumers from adulterated and misbranded dietary supplements due to improper manufacturing, packaging, or holding practices. By observing CGMP regulations that require that dietary ingredients and dietary supplements are manufactured, packaged, or held in a controlled environment, manufacturers can ensure that dietary ingredients and dietary supplements are not adulterated or misbranded during manufacturing, packaging, and holding operations. Manufacturing, packaging, and holding dietary ingredients and dietary supplements under CGMPs will provide consumers with greater confidence that dietary supplements contain the dietary ingredients that they are supposed to contain and that these dietary ingredients were evaluated for their identity, purity, quality, strength, or composition. The CGMP regulations, if finalized as proposed, would require a manufacturer to establish specifications for the dietary ingredients and dietary supplements that it makes. Thus, under the proposed CGMPs, a dietary supplement with a particular

dietary ingredient listed on its label must contain that particular dietary ingredient. Moreover, that dietary ingredient must meet certain specifications that the manufacturer establishes as to the purity, quality, strength, and composition. CGMPs are intended to ensure that a dietary supplement contains what the label says it contains. If it does not, the dietary supplement would not only be misbranded under section 403 of the act, but also would be adulterated under section 402(g) of the act.

3. What Definitions Apply to this Part? (Proposed § 111.3)

Proposed § 111.3 defines various terms used in proposed part 111. In general, we have used definitions that are similar to definitions in part 110 for food and other CGMP regulations. However, we have modified some definitions for "plain language" purposes under the presidential "plain language" memorandum (Ref. 43) and to make other definitions more appropriate for dietary ingredients and dietary supplements.

In some cases, we based a definition on provisions in the industry outline published in the ANPRM. However, we did not adopt all of the definitions in the industry outline. For example, the industry outline defined terms such as, "adequate," "composition," "raw material," "representable sample," and "rework." We omitted those definitions from this proposal because the terms are generally understood, or because

definitions for those terms are unnecessary for purposes of understanding the proposed rule.

Proposed § 111.3 states that the definitions and interpretations of terms in section 201 of the act apply to such terms when used in these regulations. Section 201 of the act defines various terms that appear throughout the act, including "dietary supplement" (see section 201(ff) of the act). Other terms in section 201 of the act, such as "label" (section 201(k) of the act) and "pesticide chemical" (section 201(q)(1) of the act), have a long history of use. The definitions and interpretations of such terms apply when we use those terms in this rule.

Proposed § 111.3 defines specific terms used in the proposal.

Proposed § 111.3 defines "batch" as "a specific quantity of a dietary ingredient or dietary supplement that is intended to meet specifications for identity, purity, quality, strength, and composition, and is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture."

The phrase "identity, purity, quality, strength, and composition," means that the production on a batch-by-batch basis is consistent with the master manufacturing record and is what it is represented on the label to be (identity); is without impurities and is the desired product (purity); is the identity,

purity, and strength for its intended purpose (quality); is the concentration, that is, the amount per unit of use intended (strength); and is the intended mix of product and product-related substances (composition).

Proposed § 111.3 defines "batch number, lot number, or control number" as "any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, or holding of a batch or lot of dietary ingredients or dietary supplements can be determined." You should note that the proposed definition would have the batch, lot, or control number be "distinctive," which means, for the purposes of this proposal, that it is unique in some fashion, and is not a reused number. Numbers must be distinctive because, if a problem involving a marketed dietary ingredient or dietary supplement later results, a distinctive batch number will make it possible for you to investigate the source of the problem and the manufacturing history for the batch. This would help you to take appropriate actions concerning that batch more quickly.

Proposed § 111.3 defines "component" as "any substance intended for use in the manufacture of a dietary ingredient or dietary supplement including those that may not appear in the finished dietary ingredient or dietary supplement." Proposed § 111.3 states that "component" includes ingredients and dietary ingredients as described in section 201(ff) of the act. Under

proposed § 111.3, components would include ingredients, dietary ingredients, manufacturing aids (such as solvents that are removed during manufacturing), and reagents that are used to synthesize a product.

Under the proposed definition of "component," a component may or may not appear in the finished product. For example, solvents that are used to produce herbal extracts do not necessarily appear in a finished dietary supplement, but the proposed rule still would consider the solvents to be "components." As another example, ingredients, such as cellulose (which is used to make tablets) or gelatin (which is used to make capsules), might be used to produce dietary supplements; these ingredients remain in the finished product, but would be "components" under the proposed rule.

Proposed § 111.3 defines "consumer complaint" as:

> * * * communication that contains any allegation, written or oral, expressing dissatisfaction with the quality of a dietary ingredient or a dietary supplement related to good manufacturing practices. Examples of product quality related to good manufacturing practices are: Foul odor, off taste, superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g.,

> bacteria, pesticide, mycotoxin, glass, lead), 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. Because an ingredient is defined as a substance that is intended to be present in the finished dietary ingredient or dietary supplement and a component is defined as a substance that may or may not be included in the finished dietary ingredient or dietary supplement, all ingredients are components but not all components are ingredients.

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 "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.

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.

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 may raise 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 may be 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; and
2. At any 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. 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. If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than

those we have provided, the comments should so state and provide an explanation.

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. 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. In order to limit the burden to manufacturers, FDA is not proposing such requirements. However, 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 who 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 written procedures for maintenance, cleaning, and sanitation should be required in a final rule. If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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. 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. We seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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.