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## Part II

# Department of Health and Human Services

**Food and Drug Administration**

**21 CFR Parts 111 and 112**

**Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule**

**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 or electronic comments by June 11, 2003. Submit written or electronic comments on the collection of information by April 14, 2003.

**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.*

**FOR FURTHER INFORMATION CONTACT:** Karen Strauss, Center for Food Safety and Applied Nutrition (HFS–821), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–2375.

**SUPPLEMENTARY INFORMATION:**

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## I. Background

### *A. Dietary Supplement Health and Education Act (DSHEA)*

DSHEA (Pub. L. 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/chondroitin, 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 documenting 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 for 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.

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

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

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

To show how proposed § 111.25(a)(1) might apply, assume that you use a mixer to blend powdered ingredients. If the mixer blade is too small, it might not mix the ingredients properly or thoroughly, and the resulting batches might be adulterated if the ingredients are not provided at the required levels throughout the batch. In this example, the mixer was not suited for its intended use. As another example, if your manufacturing equipment is so complex or designed in a way that makes cleaning difficult, any unclean surfaces on that equipment could become a source of contamination in the future. In this case, the equipment was not adequately cleaned and properly maintained or, alternatively, was not of appropriate design for its intended uses.

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

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

• Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;
• Corrosion-resistant if the equipment or utensils contact components, dietary ingredients, or dietary supplements;
• Made of nontoxic materials;
• Designed and constructed to withstand the environment of their intended use, the action of components, dietary ingredients, or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and
• Maintained to protect components, dietary ingredients, and dietary supplements from being contaminated by any source.

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

and utensils to guard against contamination.

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

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

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

Proposed § 111.25(a)(6) would require instruments or controls used in the manufacturing, packaging, or holding of a dietary ingredient or dietary supplement to be accurate and precise, adequately maintained, and adequate in number for their designated uses. By using the words, ''accurate and precise,'' we mean that the instruments or controls must be accurate—the recorded measurements are equal to the true value of the thing being measured—and precise—individual measurements should be close to each other when made under the same conditions. For example, if the temperature inside a particular piece of equipment is 100 °F, and your thermometer for that piece of equipment reads a temperature of 100 °F, the thermometer is accurate. If multiple temperature readings for that thermometer ranged from 99.7 °F to 100.4 °F, and the variation in temperature was not significant statistically, you could say the thermometer is precise. The proposed requirement identifies examples of such instruments and controls, such as instruments or controls you use to measure, regulate, or record:

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

Instruments or controls that affect the environment, such as instruments that regulate temperature, pH, and water activity, are important because environmental factors can influence microorganism growth and deterioration. For example, changes in water activity ($a_w$) can have a dramatic impact on microorganism growth. A population of *Salmonella typhimurium* is reduced tenfold in 0.18 minutes at 60 °C if the $a_w$ for the suspending medium is 0.995. If the $a_w$ is 0.94, it takes 4.3 minutes (or nearly 24 times as long) at 60 °C to achieve the same tenfold reduction (Ref. 58).

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

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

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

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

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

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

the risk that such contaminants will enter the compressed air or other gases.

Proposed § 111.25(b)(1) would require that you calibrate your instruments and controls that you use in manufacturing or testing components, dietary ingredients, or dietary supplements. Proposed § 111.25(b)(2) would require that you calibrate before you first use the instruments and controls and either as specified in writing by the manufacturer of the instrument and control or at routine intervals or as otherwise necessary to ensure their accuracy and precision. Calibrating instruments and controls will ensure that they are accurate and precise and that the instrument or control readings are ''true values.'' We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for calibrating instruments and controls, and whether there are other procedures, that we should consider including in a final rule. 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.

Proposed § 111.25(c) would require that you must establish a written procedure for calibrating instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement and document that the written procedure was followed each time a calibration was performed or that you must document, at the time of performance, that the instrument and control calibration established in accordance with this section was performed. The proposed calibration requirement gives you discretion in deciding whether to establish and follow a written calibration procedure. If you establish a written procedure for calibrating instruments and controls, you must document, at the time of calibration performance, that the written procedure was performed. If you do not establish a written calibration procedure then you must document, at the time of performance, that the calibration established accordance with this section was performed. You must identify the following for calibrating instruments and controls in any written procedure or at the time of performance:

- The instrument or control calibrated;
- The date of calibration;
- The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy. A certification of accuracy usually accompanies a standard reference material and often is valid for a specific period of time, but the supplier of the reference standard may recertify the standard's accuracy. The recertification typically involves testing by the supplier to verify that the material maintains accuracy as a testing reference. This information also may help you trace the source of a problem, if one arises, in your dietary ingredients or dietary supplements. For example, if consumers report an adverse event with a batch of dietary supplements, records containing a certification of accuracy of the reference standards used and a history of their recertification would help you determine if the problem resulted from using an inaccurate reference standard to calibrate your instruments;
- The calibration method used including appropriate limits for accuracy and precision of instruments and controls when calibrating;
- The calibration reading or readings found;
- The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and
- The initials of the person who performed the calibration.

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

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

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

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

necessary, and allow them to dry thoroughly before you use them again.

Thoroughly drying equipment before it is used for manufacturing or holding dry dietary products is essential to ensure that the equipment will not change the composition of the dry product. For example, if moisture is left on equipment, the moisture will become a part of the product and may change the composition of the product. Moist surfaces can also promote microorganism growth, and microorganisms can adulterate your components, dietary ingredients, or dietary supplements.

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

Proposed § 111.25(e)(4) would complement proposed § 111.25(e)(2) and (e)(3) by requiring that you clean, as frequently as necessary, surfaces that do not touch components, dietary ingredients, or dietary supplements to protect against contamination. For example, you would not have to clean your ceilings as often as you clean your contact surfaces because your ceilings normally do not touch components, dietary ingredients, or dietary supplements. However, you would have to clean your ceilings as frequently as necessary to prevent dust or other contaminants from falling onto your components, dietary ingredients, dietary supplements, and contact surfaces.

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

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

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

We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for maintenance, cleaning, and sanitizing. Further, we invite comment on whether we should require that the person who performs the maintenance, cleaning, and sanitizing described in this section document, at the time of performance that the maintenance, cleaning, and sanitizing were performed. Those procedures may be helpful to inform you that equipment is being maintained, cleaned, and sanitized regularly and as frequently as is necessary based on the actual use, as opposed to the planned use, of the equipment. 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.

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

Proposed § 111.25(f) would require that you keep calibration records as required by this section in accordance with the recordkeeping requirements in proposed § 111.125. Such records will verify for you and the agency that calibrations are performed. More importantly, these records will help you ensure that all calibrations are performed. If problems do occur with the production of a product, these records will help you determine whether those problems are associated with faulty calibrations. These records will help you determine which batches were produced under these conditions. Further, these records will help you train employees or adjust the calibration schedule as needed to avoid further problems.

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

Manufacturers of dietary ingredients and dietary supplements often rely on automatic, mechanical, and electronic

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

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

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

Proposed § 111.30(a)(2) would require that you determine the suitability of your equipment. The equipment that you use must be capable of operating satisfactorily within the operating limits required by the process. The equipment must function as intended. Some systems may work properly only within a narrow range of environmental conditions, such as temperature and humidity, and some might be particularly sensitive to electromagnetic interference. The actual conditions of use of a system should be considered as early as possible in its design and development. Systems need to be installed in a manner that takes into account the inherent limitations of the system, tested under conditions that reflect actual conditions of use, and properly maintained to ensure that they continue to function as expected during their lifetime.

Moreover, the incorporation of software into the operation of automatic equipment has not only increased the complexity of such equipment but also has resulted in a process that may operate differently for each execution because a software-based control system can be configured at will by the operator or by the system itself. Therefore, proposed § 111.30(a) would require that you exercise appropriate controls over systems and, in particular, over the software used in the systems.

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

- Routinely calibrate, inspect, or check to ensure proper performance.
- Make and keep written records of equipment calibrations, inspections, or checks;
- Establish and use appropriate controls to ensure that your quality control unit approves changes in master manufacturing record, batch control records, packaging operations and label operations, or changes related to the equipment that you use and that only authorized personnel institute the changes;
- Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use and have your quality control unit approve these controls; and
- Make and keep backup file(s) of software programs and of data entered into your computer system. Your backup file may be a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks but must be an exact and complete record of the data you entered. We also propose to require that you keep your backup software programs and data secure from alterations, inadvertent erasures, or loss. In this way, you have a record of changes to your software program and of your current software program used in manufacturing. This information is important to both identify any production errors or discrepancies and to make necessary corrections. Such records will allow you to troubleshoot and to operate these systems with a minimum of interruption when problems occur because the records will include a copy of all software used and a backup file of data entered into the computer or related system which can be used to reload the system. The records also will provide information that you can use in trying to determine why a problem with the system is occurring or why the system is not producing a dietary ingredient or dietary supplement that complies with your specifications for the product.

Appropriate controls that you establish and use for automated measuring, regulating, or recording temperatures, pH, acidity, water activity, or other conditions will minimize the potential for growth of microorganisms, for contamination, or for adding too much or too little of a dietary ingredient. Observations, inspections, and checks of the equipment will help you to determine if critical factors such as revolutions per minute, temperatures, pressures, process times, and automatic documentation are being controlled by the system. Under proposed § 111.30(b), examples of controls to ensure that the equipment functions in accordance with its intended use include:

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

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for the calibration, inspection, and checking of automatic equipment. In addition, we invite comment on whether there are procedures, other than those mentioned, 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.

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

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

We believe, in general, that scientific knowledge and industry experience have defined the basic elements of a sound verification system to include; determining whether the capacity of the hardware matches its assigned function; identifying and considering operational limits in establishing production procedures; determining whether the software matches the assigned operational function; testing simulated production conditions including ''worst case'' conditions; repeating tests enough times to assure a reasonable measure of consistent reproducible results; documenting the verification program; and initiating reverification when significant changes are made to the system or when errors are noted.

Although verification steps would vary according to the nature of the dietary supplement and the complexity of the process, the basic elements of a verification system would be generally applicable to all dietary ingredients and dietary supplements. The primary benefit of a verification system would be to provide a foundation for building a comprehensive approach to ensure that the equipment performs in a predetermined way, but verification could impose additional costs on manufacturers.

We invite comment on whether automatic, mechanical, and electronic equipment verification and reverification elements that we have discussed should be done, should be included in the final rule as requirements, which would include requirements to document the verification steps. We invite comment on whether we should regulate computerized systems separately from other automatic equipment. 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.

### *E. Production and Process Controls (Proposed Subpart E)*

Proposed subpart E contains production and process controls to help ensure that you have controls covering all manufacturing, packaging, label, and holding operations, and that those controls will prevent adulteration of your dietary ingredient or dietary supplement. We propose to establish a framework in which decisions about producing a dietary ingredient or dietary supplement are left to you, but that charges you with incorporating into your production process, measures that are designed to ensure that the dietary ingredient or dietary supplement is manufactured in a manner that will prevent adulteration and misbranding.

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

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

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

Proposed § 111.35(b) would require that your production and inprocess control system must be designed to ensure that you manufacture, package, or hold dietary ingredients or dietary

supplements in a manner that will prevent their adulteration. The proposal would require that your production and inprocess control system must include all requirements of this subpart and also would require your quality control unit to review and approve the production and inprocess control system. We believe that requiring a production and inprocess control system is necessary to provide consistency in producing different batches of dietary ingredients or dietary supplements and to facilitate preparing each batch.

Proposed § 111.35(c) would require that you use your quality control unit in your manufacturing, packaging, and label operations to ensure that these operations are performed in a manner that prevents adulteration and to ensure that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

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

A ''dietary ingredient'' within the meaning of section 201(ff) of the act that is in, or intended for use in, a dietary supplement is exempt from the definition of ''food additive'' in section 201(s). Such ''dietary ingredients'' are not subject to the premarket approval standard for food additives under section 409 of the act. However, under section 402(f)(1) of the act, in order for a dietary ingredient or a dietary supplement not to be deemed adulterated, substances that are ''dietary ingredients'' that are used in the manufacture of a dietary ingredient or a dietary supplement must not present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling or, if no such labeling, under ordinary conditions of use. In addition, there must be adequate information to provide reasonable assurance that a new dietary ingredient does not present a significant or unreasonable risk of illness or injury. Further, under section 402(f)(1) of the act, dietary ingredients must not be poisonous or deleterious substances within the meaning of section 402(a)(1) of the act. Thus, manufacturers have a responsibility to ensure that the dietary ingredients and dietary supplements that they produce are not adulterated under section 402(f) of the act.

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

Proposed § 111.35(d) would require that any substance, other than a ''dietary ingredient,'' the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement, must be:

- Authorized for use as a food additive under section 409 of the act, or
- Authorized by a prior sanction consistent with 21 CFR 170.3(l), or
- If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement, or
- Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of section 201(ff) of the act, must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement, and
- Must comply with all other applicable statutory and regulatory requirements under the act.

Thus, if a color additive is used in a dietary ingredient or dietary supplement, it must be listed in Title 21 of the Code of Federal Regulations (CFR) for use in food and the listing must, by its terms, include such use in a dietary supplement. If the substance is not a color additive, it must be safe under other relevant sections of the act. Relevant considerations about the safety of a substance that may be used as an ingredient (other than a ''dietary ingredient'' under section 201(ff) of the act) in a dietary ingredient or a dietary supplement would include the amounts of the substance that likely would be ingested, based on the amounts recommended or suggested in the label, or under ordinary conditions of use. Such a use may present concerns about the safety of exposure to such ingredient, based on the chronic use suggested or reasonably expected. Therefore, it is incumbent on the manufacturer to use ''non-dietary ingredients,'' that are safe and lawful under applicable sections of the act for such use.

As stated previously, ingredients used in dietary ingredients or dietary supplements, other than color additives, are required to be approved for use as a food additive unless excepted from the definition of a food additive under section 201(s) of the act. For example, we approved the use of sucralose as a general purpose sweetener in food, which would include its use in a dietary ingredient or dietary supplement (64 FR 43908, August 12, 1999). Some other current food additive listings that would include uses in certain types of dietary supplements include, ethyl cellulose (21 CFR 172.868) as a component of protective coatings for vitamin and mineral tablets, and hydroxypropyl cellulose (21 CFR 172.870) as a binder and disintegrator in dietary supplement vitamin or mineral tablets or wafers. If you have questions about the regulatory status of any substances that you want to use in a dietary ingredient or a dietary supplement, you are encouraged to contact CFSAN's Office of Food Additive Safety.

We recognize that some ingredients may not be subject to section 409 of the act, food additive approval, because they are GRAS substances. For those substances that are GRAS, proposed § 111.35(d)(4) would require the manufacturer to have documentation for the basis for why such a substance, that is not a ''dietary ingredient'' within the meaning of section 201(ff) of the act, is approved for use or is GRAS for use in a dietary ingredient or dietary supplement.

The statute, under section 402(g)(2) of the act, provides that the Secretary may by regulation prescribe good manufacturing practices for dietary supplements. If the good manufacturing practices are not met, the dietary ingredient or dietary supplement would be adulterated under section 402(g) of the act. Under proposed § 111.35(d), substances that are not ''dietary ingredients'' that are used in dietary ingredients and dietary supplements must be safe and lawful to comply with CGMPs for such products. Thus, these

nondietary ingredient substances must be subject to a food additive listing, authorized by a prior sanction, included with the terms of a color additive listing, or listed as GRAS for such use in 21 CFR part 182 or affirmed as GRAS for such use in 21 CFR part 184. Alternatively, you can meet the requirements of § 111.35(d) by a showing that the substance is GRAS within the meaning of § 170.30 (21 CFR 170.30).

Proposed § 111.35(d)(4) would require that you have information in your files that would substantiate the GRAS status of any nondietary ingredient substance that is not otherwise the subject of a food additive approval, prior sanction, or color additive listing. We believe that, to implement the act in a way to ensure that the statutory goals are achieved; that is, to ensure that the manufacturer has the relevant information to ensure that any asserted GRAS ingredient is, in fact, GRAS, it is appropriate to require that you maintain, in your files, the basis for why the nondietary substance you assert is GRAS that you use in a dietary ingredient or dietary supplement is, in fact, GRAS. You must not use unsafe ingredients in your products. Therefore, you must have information on ingredients that you intend to use in a dietary ingredient or dietary supplement to demonstrate that such ingredient is safe. Otherwise, as a responsible manufacturer, you would not use the ingredient in your product.

Therefore, under proposed § 111.35(d)(4), for any claim that a nondietary ingredient in a dietary supplement is GRAS, you must support such claim with a cite to a FDA regulation or an explanation for why there is general recognition of the safety of the use of the substance in a dietary ingredient or dietary supplement. If such claim is based on general recognition of safety based on scientific procedures, the explanation would be based on evidence that demonstrates that there is common knowledge about the safety of the substance throughout the scientific community knowledgeable about the safety of such substance. Under § 170.30(c)(1), if a substance is GRAS based on common use in food prior to January 1, 1958, this determination must be based solely on food use of the substance before January 1, 1958, and ordinarily must be based upon generally available data and information. Thus, GRAS based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation. If you wish to use an ingredient based solely on food use of the substance prior to January 1, 1958, you would need to support a claim that the ingredient is GRAS with an explanation of the basis for why the ingredient was in common use in a dietary ingredient or a dietary supplement prior to January 1, 1958, and why that use provides the basis for general recognition of the safety of the substance.

We will view any ingredient, that cannot meet the standard of § 170.30 for a GRAS determination, as a food additive, and any dietary ingredient or dietary supplement that contains a food additive that we have not approved for use in the dietary ingredient or dietary supplement is subject to regulatory action. If the safety of such ingredient is not recognized expressly in an FDA regulation, you have the burden to explain why the ingredient is GRAS under § 170.30.

In the **Federal Register** of April 17, 1997, we issued a proposed rule on GRAS notification (62 FR 18938). We are currently accepting GRAS notifications under this proposed rule. However, we recognized in the GRAS notification proposal (62 FR 18938 at 18951) that a failure by us to object to a GRAS notification is not equivalent to a GRAS affirmation of GRAS status and we, as a matter of discretion, may not advise a notifier of a problem that we have identified that raises no important public health issues. Therefore, if you submit a GRAS notification to us under the April 17, 1997, proposed rule, our failure to object to your determination that an ingredient is GRAS in a dietary ingredient or dietary supplement will not constitute a GRAS affirmation by us. Further, if we know of no reason to question the safety and lawfulness of the ingredient that is the subject of a GRAS notification and that is used in the manufacture of a dietary ingredient or dietary supplement, we would not object to your reliance on your determination that the use of the substance is GRAS. You could not use our response to your GRAS notification as your basis for asserting compliance with the requirements under proposed § 111.35(d) because an FDA response letter to a GRAS notification is not the same as your explanation, *e.g.*, a response letter does not provide an explanation for why an ingredient is GRAS. We encourage any dietary ingredient or dietary supplement manufacturer to consult with us on any ''nondietary ingredient'' substance that it intends to use in such product to ascertain whether the use of such ingredient may be more appropriately submitted for review by us in a food additive petition.

Proposed § 111.35(e) would require that you establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. These points, steps, or stages may include heating steps, cooling steps, points where specific sanitation procedures are needed, product formulation control steps, points where cross contamination may occur, and steps where employee and environmental hygiene are necessary to prevent adulteration of the dietary ingredient or dietary supplement. These specifications are regulatory specifications and you would be required to perform testing or examination to confirm such regulatory specifications are met. We discuss performing testing or examination to confirm that a regulatory specification is met later in this document. A deviation from such specification would signify that the dietary ingredient or dietary supplement could be adulterated. Such deviation would require investigation and a disposition decision approved by the quality control unit under proposed § 111.35(i) (which we also discuss later in this document).

The proposed rule would not prevent you from establishing additional specifications that are not at points, steps, or stages where control is necessary to prevent adulteration if those additional specifications will help you meet your quality control demands, but a failure to meet those nonregulatory specifications will not require that you make a material review and disposition decision. In other words, you may establish additional specifications beyond those that the proposed rule would require, and a material review and disposition decision would be needed only for those specifications if not met, that are required under the proposed rule. For example, if you determine that a specific heat temperature is needed at a point, step, or stage in the manufacturing process to prevent adulteration, that heat temperature specification is a general regulatory specification. If not met, you would need to make a material review and disposition decision.

In addition, proposed § 111.35(e) identifies certain points, steps, or stages where a regulatory specification is required. Regulatory specifications are required for materials that you receive, at the inprocess stage, and that you manufacture, *e.g.*, at the finished product stage. Specifically, we are proposing to require that you establish specifications at these control points for the identity, purity, quality, strength,

and composition of the components (upon receipt only) and for dietary ingredients or dietary supplements (at all of these control points).

You may establish additional specifications (*i.e.*, those in addition to identity, purity, quality, strength, and composition) at these same control points. For example, you may determine that an inprocess specification is necessary during the manufacturing process to prevent adulteration. That inprocess specification would be a regulatory specification. Specifications also are needed for the inprocess materials to ensure that inprocess materials are not adulterated by the manufacturing process and are in compliance with the master manufacturing record. Additional specifications also may be needed for the finished product stage. Specifications are needed for dietary ingredients and dietary supplements you manufacture to ensure that the manufacturing process produces the correct dietary ingredient or dietary supplement and that adulterated and misbranded dietary supplements do not reach the marketplace.

Containers and closures are a form of packaging. The containers and closure or other packaging, such as blister pack, that comes in contact with dietary ingredients or dietary supplements must not be reactive or absorptive so as to affect the safety of the dietary ingredient or dietary supplement and must be composed of substances that are authorized by the agency for use as a food additive, the subject of a valid notification under section 409 of the act, authorized by a prior sanction issued by the agency, or GRAS for such use.

Thus, under this proposed requirement, you would be required to establish specifications for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. Specific specifications that would be required for you to establish include:

- The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;
- The inprocess controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;
- The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and
- The packaging that may come in contact with dietary ingredients and dietary supplements. The packaging must be safe and suitable for its intended use and comply with all other applicable statutory and regulatory requirements under the act and must not be reactive or absorptive so as to affect the safety of the dietary ingredient and dietary supplement.

Proposed § 111.35(f) would require that, for each point, step, or stage, for which a specification is established under proposed § 111.35(e), you must monitor the production and inprocess control points, steps, or stages to ensure that they meet specifications and to detect any unanticipated occurrence that may result in adulteration. Regular monitoring of these points is necessary to ensure that the product meets the specifications under proposed § 111.35(e) and to ensure that any trend toward loss of control is quickly identified. Quick identification of any trends that may lead to a deviation from a specification could mean that adjustments may be made to prevent a deviation from occurring. In the event that a deviation or unexpected occurrence (such as leakage from a pipe onto a component) occurs, effective corrective actions can be taken to remove the adulterated product from the system.

Under proposed § 111.35(g) you must ensure through testing or examination that each specification that you establish under § 111.35(e) is met. Under § 111.35(e), you would have to determine the points, steps, or stages where control is necessary to prevent adulteration. However, there are certain points, steps, or stages in proposed § 111.35(e) that we tentatively have determined to be those where control is necessary to prevent adulteration. Specifically, we tentatively have determined that such control points include the receipt of components, dietary ingredients, or dietary supplements, the inprocess stage of manufacturing, and the finished product batch stage. Further, we tentatively have determined that at each of those control points, there need to be specifications for the identity, purity, quality, strength, and composition of components (only at receipt stage for components), dietary ingredients and dietary supplements (at all of these control points). In addition, we tentatively have determined that specifications are necessary for dietary ingredient and dietary supplement labels and packaging.

The testing and examination requirements in proposed § 111.35(g) would require that you conduct a test or examination to ensure that specifications that you established are met; *i.e.*, that you conduct a test or examination at those points, steps, or stages in the manufacturing process where you determined that a specification is needed to ensure that the specification, in fact, is met. For certain specifications that we would require, *i.e.*, the identity, purity, quality, strength, and composition upon receipt, inprocess, and at the finished product batch stage, we are providing some flexibility for testing. To illustrate, testing or examination requirements for specifications that you establish (*e.g.*, those other than the identity, purity, quality, strength, and composition of the dietary ingredients or dietary supplements received; inprocess, or finished product), such as for a botanical extraction process that uses a specific heat temperature for spray drying, you would be required to ensure by testing or examination that the specified temperature was used. You would be required to perform such a test or examination at the inprocess point, step, or stages where control is necessary. As another example, if a specific temperature is used on a finished batch of dietary ingredient or dietary supplement as a heat treatment to inactivate or remove objectionable microorganisms that pose a health hazard, and thus, the heat treatment temperature is a critical control point specification, then you must perform testing or examination to determine that the specific temperature was used. You would be required to perform such a test on each finished batch of dietary ingredient or dietary supplement that is manufactured.

For those specifications that we tentatively have determined are necessary (identity, purity, quality, strength, and composition) at receipt, inprocess, and finished product stage, we are proposing specific testing requirements that provide some flexibility. Under § 111.35(g)(1), we would require that you test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to confirm that specifications are met for the identity, purity, quality, strength, and composition intended, provided that there are scientifically valid analytical methods available to perform such testing. We recognize that certain tests for identity, purity, quality, strength, or composition for certain finished product may not be available due to complex finished matrices that would make such testing impracticable. Further, even though there may not be a scientifically valid analytical method that you could use to provide you with the information to evaluate, for example, the identity and composition of the finished

product, there may be methods available for testing at the finished product stage for other required specifications of purity, quality, and strength. Under proposed § 111.35(g)(3), your quality control must document that a scientifically valid analytical method is not available to perform finished product testing for any one of the required specifications for identity, purity, quality, strength or composition. If your quality control unit documents that a scientifically valid analytical method for testing each batch of dietary ingredient or dietary supplement is not available for any one of those required specifications, then you would be required, under § 111.35(g)(2)(i) and (g)(2)(ii) to test incoming shipment lots of components, dietary ingredients, or dietary supplements for any such specification to determine whether it is met and to test inprocess for any such specification in accordance with the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements.

Using a supplier certification, guarantee, or certification in lieu of performing testing on each shipment lot of components, dietary ingredients, or dietary supplements required in accordance with this section is not appropriate because it is possible that a supplier's certification or guarantee may not ensure the identity, purity, quality, strength, or composition of a component, dietary ingredient or dietary supplement. For example, a supplier of the dietary ingredient plantain provided a ''certificate of analysis'' indicating that the plant material was plantain powder, with a description of certain of its physical characteristics (Ref. 6). The plantain was contaminated with *D. lanata* (a plant that contains powerful heart stimulants that can cause life-threatening reactions including cardiac arrest, if ingested) and was distributed to at least 150 manufacturers, distributors, and retailers. Thus, if you do not perform finished product testing under § 111.35(g)(1) for identity, purity, quality, strength, or composition, then you would need to test for that nontested finished product specification upon receipt and inprocess as specified in the master manufacturing record to ensure that adulterated dietary ingredients or dietary supplements are not distributed to the marketplace.

If you are able to perform testing on each finished batch of dietary ingredient or dietary supplement to confirm that specifications are met for the identity, purity, quality, strength, and composition intended, then we would recommend, but would not require, that you also test materials received for these same specifications to ensure that they are the right ingredients and so that you do not end up having to destroy an entire batch of finished product after using an erroneous ingredient that could have otherwise been identified earlier before being added to a batch.

For example, if you manufacture a batch of dietary supplements that contains only one single dietary ingredient, St. John's Wort extract (*Hypericum perforatum*), and there are scientifically valid analytical methods available to test the finished dietary ingredient or supplement to confirm that the specifications are met for the identity, purity, quality, strength, and composition intended, then you must test each batch using such methods. In this example, you would not be required to perform testing of incoming shipment lots of St. John's Wort to confirm identity, purity, quality, strength, and composition to confirm that specifications are met nor would you be required to perform testing of inprocess for these same specifications in accordance with the master manufacturing record. As discussed later under proposed § 111.40(b)(2), although testing would not be needed at receipt stage for identity, purity, quality, strength, and composition, you would be required under that section, to visually compare the label, supplier's invoice, guarantee, or certification with your purchase order for consistency. In another example, if you manufacture a dietary supplement that contains multiple dietary ingredients (*e.g.*, Ginkgo Biloba, vitamin C, and folic acid) and you do not perform testing on the finished dietary supplement because there are not scientifically valid analytical methods available to confirm that the specifications for identity, purity, quality, strength, and composition are met for each dietary ingredient in the finished batch mixture, then you would be required to perform testing of incoming shipment lots of each dietary ingredient to confirm that such specifications are met and perform inprocess testing in accordance with the master manufacturing record to ensure that such specifications are met. Thus, the proposed testing requirements provide flexibility for testing for identity, purity, quality, strength, and composition, based on the availability of scientifically valid testing methods to perform testing on each batch of dietary ingredients or dietary supplements.

Proposed § 111.35(h) would require that you use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method. If there is an AOAC or FDA method available that is appropriate for your purpose, you should use that test method. For example, if your dietary supplement claims to contain vitamin C, there is a specific test for identifying vitamin C, and so proposed § 111.35(h) would require that you use that test (Ref. 68). If an AOAC or FDA method is not available, a scientifically valid analytical method is one that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research. While there may not be an AOAC or FDA method available, we are not aware of a situation where an appropriate scientifically valid analytical method is not available. You could perform the tests yourself or have someone perform these tests for you.

Proposed § 111.35(i) would require that you must:

- Establish corrective action plans for use when an established specification is not met. We believe that this requirement is necessary because you may need to take corrective action quickly, and the best way to ensure that a corrective action is appropriate is to determine the action in advance. For example, if, during the production of a specific batch, the temperature specified for tablet coating drying is not met, you would be able to consult the corrective action plan to see whom you should contact, what correction to make, and when to make the correction. Having corrective action plans in place before a problem occurs can help you deal with those problems quickly and efficiently. As another example, if during production an operator notes that too low a temperature is used during a tablet coating drying operation, it would be best for the operator to have an action plan for immediate implementation, rather than having to stop the drying process to wait for instructions on what to do. Quick action may reduce the possibility of diminished changes in tablet dissolution or an adulterated product and enable you to avoid having to destroy incorrect tablets that are too moist or clump together or to avoid recalling a product because it settled into a clump or became moldy in the container;
- Review the results of the monitoring required by this section and conduct a material review of any component, dietary ingredient, dietary supplement, packaging or label for which you establish a specification that is not met, or any unanticipated occurrence that adulterates or could result in adulteration of the component,

dietary ingredient, dietary supplement, packaging, or label. This review will reveal whether the monitoring is actually being done and being done correctly, and whether the specifications are being met; and

• Make a material disposition decision for any component, dietary ingredient, dietary supplement, packaging, or label if:

1. A component, dietary ingredient, dietary supplement, packaging, or label fails to meet specifications;

2. Any step established in the master manufacturing record is not completed;

3. There is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label; or

4. Calibration of an instrument or control suggests a problem that may have caused batches of a dietary ingredient or dietary supplement to become adulterated; and

5. A dietary ingredient or dietary supplement is returned.

• Have your quality control unit approve any material review and disposition decision.

You should review the public health significance of any deviations from specifications or of any unexpected occurrences to ensure that dietary ingredients and dietary supplements that may have been affected adversely by a deviation do not enter the marketplace. A material review and disposition decision would ensure that the disruption of a manufacturer's business is minimized when a deviation does occur. For example, if review of a dietary supplement formulation does not contain the required identity, purity, quality, strength, or composition, you can take steps to dispose of the formulation before it is packaged and labeled. If the monitoring records are not reviewed, a dietary supplement made with a deficient formulation may be placed on the market, and a costly and embarrassing recall may be necessary.

Proposed § 111.35(i)(4) would require that for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, the proposal would require that you reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that inprocess adjustments are possible to correct the deviation or occurrence. You would be able to reprocess a rejected component, dietary ingredient, or dietary supplement if the quality control unit approves such reprocessing. However, the proposal states that you must not reprocess any component, dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms or other contaminants, such as heavy metals. We propose to prohibit reprocessing in such cases because it is unlikely that reprocessing will eliminate such forms of contamination or will eliminate such contamination without adversely affecting the component, dietary ingredient, or dietary supplement.

Proposed § 111.35(i)(5) would require that this review be conducted by an individual from the quality control unit. This is necessary to ensure that the review is conducted by a person who is qualified by training and experience to conduct such reviews and who understands the production and inprocess control system, understands the significance of a processing deviation, and knows how to respond to a deviation. This will ensure that the review that is conducted and the response to any deviation is appropriate. The requirements of this section do not mean that the manufacturer needs a large number of employees.

Proposed § 111.35(j) would require the person who conducts the material review and makes the disposition decision to document, at the time of performance, every material review and disposition decision in proposed § 111.35(i). The documentation must be included in the batch production record. Proposed § 111.35(j) would require this documentation to:

• Identify the specific deviation from the specification or the unanticipated occurrence;

• Describe your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

• Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration;

• Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence; and

• Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label. For example, did you segregate the component? Did you quarantine it until the quality control unit decided whether it should be returned to its supplier, reprocessed, or destroyed?

Proposed § 111.35(k) would require that you test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration.

The proposal also would require that you use an appropriate scientifically valid methodology for the test or examination. We discuss analytical methods in more detail elsewhere in this document in our discussion of laboratory operations, proposed § 111.60. The types of contamination covered by proposed § 111.35(k) include, but are not limited to, the following:

• Filth, insects, or other extraneous material;

• Microorganisms; and

• Toxic substances.

Under this proposed requirement, you must test or examine for those types of contamination that may adulterate or may lead to adulteration. The words, ''for those types of contamination that may adulterate or may lead to adulteration,'' at least in part, mean that you must test a botanical for filth and microorganisms of public health significance. For example, it is highly likely or certain that botanical components would be contaminated with filth and undesirable microorganisms of public health significance based on the areas in which they are harvested. Therefore, it would be inappropriate if you did not test botanical components for filth and microorganisms. The types of tests and when to test would be left to your discretion. The proposed rule would not specify any particular test or examination, so you would be able to decide on the appropriate methods for testing or examination that are suited to your components, dietary ingredients, and dietary supplements.

Contamination also can create conditions that promote further contamination by other organisms. For example, contamination resulting from possible fungal growth on a botanical component can provide the environment for mycotoxin production, especially aflatoxin (Refs. 63 and 64). Therefore, if a toxic substance is a type of contamination that may adulterate or lead to adulteration of the dietary ingredient or dietary supplement, you must perform an appropriate test to detect the toxic substance.

In other cases, a certain amount of micro flora on a botanical may be unavoidable. For example, some botanical components always will contain a certain number of microorganisms that live on the plant or come from other organisms (micro flora) on the plant. Processing these components may destroy a substantial number of the microorganisms, but some may survive processing (Ref. 65).

Therefore, for natural products it may be appropriate to perform tests of finished product to confirm that, of the microorganisms present, those of public health significance did not survive processing and those that remain that are not of public health significance do not contaminate the dietary ingredient or dietary supplement.

Although the proposal does not specify microbial limits for undesirable microorganisms, other non-FDA sources have established acceptable, general limits of microbial levels for dietary ingredients and dietary supplements (Refs. 66 and 67). These often include limits for total aerobic microbial count, which ranges from $10^4$ to $10^7$ per g, depending on source and nature of components; a total combined yeast and molds count, which can range from $10^3$ to $10^5$ per g, again depending on source and nature of components; and the absence of *Salmonella* species, *E. coli* and *Staphylococcus aureus.* We establish microbial limits for undesirable microorganisms based on scientific information such as literature surveys and laboratory analyses. At this time, however, we do not have sufficient information to support establishing microbial limits for undesirable microorganisms for dietary ingredients. Therefore, the proposed rule does not establish microbial limits for dietary ingredients. However, you must be aware of potential contamination, regardless of whether it is due to filth, insects, microorganisms, or toxins, and you must test or examine as appropriate components, dietary ingredients, or dietary supplements for those types of contamination that may adulterate or may lead to adulteration.

Proposed § 111.35(l) would explain that the tests you use to determine whether your components, dietary ingredients, and dietary supplements meet specifications must include at least one of the following tests: Gross organoleptic analysis, microscopic analysis, chemical analysis, or other appropriate test. These tests may vary in detail or complexity depending on the purposes of the test and the material being tested. For example, if your component is raw cranberries, and you are trying to verify that a shipment of red berries consists of raw cranberries, an organoleptic (visual test) may be sufficient (assuming that you recognize cranberries). However, if your component is a chemical substance, and you are trying to verify that a shipment of bulk powder is that chemical substance, chemical analysis may be more appropriate than an organoleptic analysis.

Proposed § 111.35(m) would require that you must record the results of all testing and examinations performed in accordance with this section. If a test or examination is performed on a production batch, you must record the test or examination result in the batch production record in accordance with § 111.50(c)(10). Your records must document whether the testing and examination demonstrates that specifications are met.

Proposed § 111.35(n) would require for any specification that is not met, that you must conduct a material review and disposition decision under § 111.35(i).

Proposed § 111.35(o) would require that you make and retain records, in accordance with proposed § 111.125, to ensure that you follow the requirements of this section. The proposal would require these records to include, but would not limit them to:

- The specifications established;
- The actual results obtained during the monitoring operation;
- Any deviation from specifications and any unanticipated occurrences;
- Any corrective actions taken;
- The disposition decisions and followup; and
- The identity of the individual qualified by training and experience who investigated any deviation from specifications or unanticipated occurrence and the identity of the individual from the quality control unit who reviewed the results of that investigation.

These records would enable you to show, and for us to determine, your compliance with proposed § 111.35. We generally determine CGMP compliance by conducting inspections, so records play an important role during those inspections in determining CGMP compliance.

2. What Requirements Apply to Quality Control? (Proposed § 111.37)

Proposed § 111.37(a) would require that you use a quality control unit to ensure that your manufacturing, packaging, label, and holding operations in the production of dietary ingredients and dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring that dietary ingredients and dietary supplements meet specifications for identity, purity, quality, strength, and composition. This requirement does not mean that the manufacturer needs a large number of employees. The manufacturing process for an ingredient or a dietary supplement can be a sophisticated process, and all organizational units that are involved in critical formulation and manufacturing steps, such as production, engineering, research, and regulatory affairs, may be included in quality control functions.

Proposed § 111.37(b) would require that your quality control unit must do the following:

- Approve or reject all process, procedures, specifications, controls, tests, and examinations, and deviations from or modifications to them that may affect the identity, purity, quality, strength, and composition of a dietary ingredient or dietary supplement;
- Determine whether all components, dietary ingredients, dietary supplements, packaging, and labels conform to their specifications;
- Approve or reject all components, dietary ingredients, dietary supplements, packaging, and labels;
- Review and approve all master manufacturing records and all modifications to the master manufacturing records;
- Review and approve all batch production-related records which include, but are not limited to, cross-referencing receiving and batch production records, approval of a material review and disposition decision, approval for reprocessing, and approval for releasing for distribution. Cross-referencing receiving and batch production records means that the quality control unit must verify that the batch record includes certain documentation of the receiving records for the components and dietary ingredients such as the unique identifier assigned to the shipment lot of components, testing results, a material review and disposition decision, if conducted, and approval for use by the quality control unit.
- Review and approve all processes for calibrating instruments or controls;
- Review all records for calibration of instruments, apparatus, gauges, and recording devices;
- Review all records for equipment calibrations, inspections, and checks;
- Review and approve all laboratory control processes and testing results;
- Review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records, approval for repackaging and relabeling, and approval for releasing for distribution;
- Collect representative samples of:

1. Each shipment lot of components, dietary ingredients, dietary supplements, packaging, and labels received for testing or examination, as needed, to determine whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications before use or for testing,

as needed, in consumer complaint investigations;

2. Inprocess materials at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;

3. Each batch of dietary ingredient or dietary supplement that is manufactured to determine, before you release it for distribution, whether it meets its specifications for identity, purity, quality, strength, and composition; and

4. Each batch of packaged and labeled dietary ingredients or dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record;

• Review and approve all material review and dispostion decisions; and

• Collect representative reserve samples of each shipment lot of components, dietary ingredients, and dietary supplements and each batch of dietary ingredient or dietary supplement. The proposal would require that you keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations, such as, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. We tentatively decide to require that you keep reserve samples for 3 years because we believe that 3 years would be a reasonable time period beyond the date of manufacture for appropriate followup of consumer complaints received during the marketing period. Because we have not proposed requirements for expiration dating of dietary supplements, we tentatively conclude that the date of manufacture is an appropriate starting time for the retention period. This requirement in proposed § 111.37(b)(11) also would require that the reserve samples be identified with the batch or lot number and consist of at least twice the quantity necessary for tests;

• Perform appropriate tests and/or examinations of:

1. Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications;

2. Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record where control is necessary to prevent adulteration;

3. Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

4. Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record;

• Review and approve all material review and disposition decisions; and

• Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

Proposed § 111.37 would impose duties on your quality control unit that are necessary to the quality control unit. The duties proposed in § 111.37 are important in any CGMP standards to ensure that the dietary ingredient or dietary supplement manufactured has the identity, purity, quality, strength, and composition intended. If a quality control unit did not do, that is, lacked the responsibility and authority to do, the actions described in proposed § 111.37, coordination between various parts of your manufacturing, packaging, or holding operation might become haphazard and the product could be adulterated. For example, if your quality control unit did not make decisions concerning use of components, dietary ingredients, and dietary supplements you receive, you could use the wrong component, or a contaminated component in manufacturing a dietary ingredient or dietary supplement. If your quality control unit makes decisions concerning releasing dietary ingredients and dietary supplements for distribution, it will prevent you from releasing for distribution an adulterated dietary ingredient or dietary supplement before the necessary tests results confirm that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

Your quality control unit must document, at the time of performance, that it performed the review, approval, or rejection requirements established in accordance with proposed § 111.37 by recording the date when the review, approval, or rejection and requirement was performed, and the signature of the person performing the requirement. As we explained elsewhere in this document, one of the ways we determine compliance with CGMP's is by conducting inspections, so records enable you to show, and for us to determine, compliance with CGMP's. We invite comment on whether we should require, in a final rule, written procedures for the quality control unit duties required in § 111.37. 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.

3. What Requirements Apply to Components, Dietary Ingredients, Dietary Supplements, Packaging, and Labels You Receive? (Proposed § 111.40)

Proposed § 111.40 would establish requirements to ensure that the components, dietary ingredients, dietary supplement, packaging, and labels you receive are, in fact, what you ordered. We are proposing these requirements because receiving the wrong materials can lead to mixups or the use of wrong materials and this could result in the manufacture of an adulterated and misbranded dietary ingredient or dietary supplement.

Proposed § 111.40(a)(1) and (a)(2) would apply to components, dietary ingredients, or dietary supplements you receive, and would require that you:

• Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container's condition has resulted in contamination or deterioration of the components, dietary ingredients, or dietary supplements;

• Visually examine the supplier's invoice, guarantee, or certification to ensure that the components, dietary ingredients, or dietary supplements are consistent with your purchase order and perform testing, as needed, under proposed § 111.35(g), to determine whether specifications are met.

We state in proposed § 111.40(a)(2) that you must perform testing ''as needed.'' This flexibility is necessary, given the proposed testing scheme in § 111.35(g). As previously discussed in proposed § 111.35(e), you must establish specifications for any points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. In addition, we propose to require, under § 111.35(e), certain

specifications, *i.e.*, identity, purity, quality, strength, and composition, for components, dietary ingredients, and dietary supplements upon receipt. However, in § 111.35(g), we are proposing to provide some flexibility for when testing is required for the identity, purity, quality, strength, and composition specifications. Specifically, if you perform finished product testing under § 111.35(g)(1) for identity, purity, quality, strength, and composition, then under § 111.40(a)(2) we would require that you visually compare the supplier's invoice, guarantee, or certification with your purchase order to confirm consistency between your order and the supplier's invoice, guarantee, or certification. You would not need to do testing upon receipt. That is why we have added language to § 111.40(a)(2) that states, ''and perform testing, as needed, to determine whether specifications are met.'' Alternatively, for specifications that you establish (*e.g.*, other than the identity, purity, quality, strength, and composition of the components, dietary ingredients or dietary supplements received), such as for a holding temperature necessary during transportation to your physical plant to avoid adulteration, you would be required to ensure by testing or examination that the specified temperature was used.

If you do not perform finished product testing under § 111.35(g)(1) for identity, purity, quality, strength, or composition, then you would need to test for that nontested finished product specification upon receipt. In that case, testing would be needed under both proposed §§ 111.35(g)(2) and 111.40(a)(2). You still would need to visually compare the supplier's invoice, guarantee, or certification with your purchase order to confirm consistency between your order and the supplier's invoice, guarantee, or certification.

Thus, for those specifications of identity, purity, quality, strength, or composition for which your quality control unit determines that you cannot test for at the finished product stage (because there are no available scientifically valid methods), then you would be required, under § 111.35(g)(2)(i) to test incoming shipment lots of components, dietary ingredients, or dietary supplements for any such specification to determine whether it is met, and such a test also would be considered to be necessary under § 111.40(a)(2). As discussed earlier, you may not rely on a supplier's certification or guaranty in lieu of such testing, and in addition to such testing, still would need to visually examine the supplier's invoice, guarantee, or certification.

Under § 111.40(b)(3) through (b)(5), we would require that you:

- Quarantine components, dietary ingredients, or dietary supplements until your quality control unit reviews the supplier's invoice, guarantee, or certification and performs testing, as needed under proposed § 111.35(g), of a representative sample to determine that specifications are met. These are the specifications that you would set in accordance with proposed § 111.35(e) and appropriate tests or examinations used in accordance with proposed § 111.35(g) for materials that you receive. If specifications are not met, proposed § 111.40(a)(3) would require that you conduct a material review and make a disposition decision. Your quality control unit must approve and release the components, dietary ingredients, and dietary supplements from quarantine before you use them;
- Identify each lot of components, dietary ingredients, or dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component or dietary supplement, and the status (*e.g.*, quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment lot received. Using a unique identifier throughout the manufacturing process will make it possible to track and account for components, dietary ingredients, and dietary supplements you receive and is necessary to conduct investigations of consumer complaints; and
- Hold components, dietary ingredients, or dietary supplements under conditions that will protect against contamination, deterioration, and avoid mixups. For example, you must segregate components that your quality control unit has not released for use from those components that have been released for use. This provision would require that you refrigerate components that are subject to contamination or deterioration without such refrigeration or that otherwise require storage at a certain temperature.

Proposed § 111.40(b) would apply to packaging and labels you receive and would require that you:

- Visually examine each container or grouping of containers in a shipment for appropriate content labels, container damage, or broken seals to determine whether the container's condition has resulted in contamination or deterioration of the packaging and labels;
- Quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met. You must conduct at least a visual identification on the containers and closures. If specifications are not met, the proposal would require that you conduct a material review and make a disposition decision and also require your quality control unit to approve and release packaging and labels from quarantine before you use them;
- Identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label, and the status (*e.g.*, quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. Like proposed § 111.40(a)(4), proposed § 111.40(b)(3) would require that you use this unique identifier whenever you record the disposition of each shipment lot received; and
- Hold packaging and labels under conditions that will protect against contamination and deterioration and avoid mixups.

Proposed § 111.40(c) deals with written documentation and records. Proposed § 111.40(c)(1) would require that the person who performs the requirements established in accordance with this section to document, at the time of performance, that he or she performed the requirements. The documentation would have to include, but not be limited to, the date that the requirement was performed; the signature of the person performing the requirement; any test results; and any material review and disposition decision conducted, and the disposition of any rejected material.

Proposed § 111.40(c)(2) would require that you keep component, dietary supplement, packaging, and label receiving records in accordance with proposed § 111.125. These records are necessary to be able to determine the source of the component, dietary ingredient, dietary supplement, packaging, and labels, so that if adulteration of dietary ingredient or dietary supplement occurs, the records will show the source of the material so that its use can be stopped. In addition, the records will show the basis on which each component, dietary ingredient, dietary supplement, packaging, or label was released for use in dietary ingredient or dietary supplement production. These records

are necessary to demonstrate compliance with the CGMP and quality control procedures.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures that implement proposed § 111.40(a) and (b). 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.

4. What Requirements Apply to Establishing a Master Manufacturing Record? (Proposed § 111.45)

Proposed § 111.45 would require that you prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement that you manufacture and for each batch size to ensure uniformity from batch to batch. A master manufacturing record is analogous to a recipe that sets forth the ingredients to use, the amounts of ingredients to use, the tests to perform, and the instructions for preparing the amount the recipe calls for, *e.g.*, 250 mg, 500 mg, vitamin C. This master manufacturing record helps ensure that you manufacture each ingredient or dietary supplement in a consistent and uniform manner. If you neglect to follow the master manufacturing record, you would not add all of the necessary components in the appropriate strength or amount, and this would result in an adulterated ingredient or dietary supplement.

Therefore, proposed § 111.45(a) is necessary to ensure that you prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement to ensure that all the necessary components as specified, and in the amounts specified, are used to manufacture each batch to ensure uniformity from batch to batch and to ensure that the dietary ingredient or dietary supplement is not adulterated. Proposed § 111.45(a)(1) and (a)(2) describe the proposed contents of the master manufacturing record. The master manufacturing record would identify specifications for the points, steps, or stages in the master manufacturing record where control is necessary to prevent adulteration, and establish controls and procedures to ensure that each batch of dietary ingredient or dietary supplement manufactured meets those specifications. For example, assume that your manufacturing process blends various ingredients in order to make a dietary supplement. Under proposed § 111.45(a), your master manufacturing record would establish controls to look at specific steps in the manufacturing process and evaluate the blends for specific ingredients to ensure that you added the correct ingredients at the correct amounts or concentrations that meet your specifications before the blend proceeds to the next manufacturing step, in accordance with the master production record. Throughout the manufacturing process, you would evaluate, as necessary, any points, steps, or stages where control is necessary to prevent adulteration to ensure that specifications established for those points, steps, or stages are met.

Proposed § 111.45(b) would establish additional requirements for the master manufacturing record. These proposed requirements would include:

- The name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size. For example, assume you have a million tablet batch size of a vitamin C product in 250 mg tablets and that the only other ingredients in your product are starch, microcrystalline cellulose, and dicalcium phosphate. Under proposed § 111.45(b)(1), your master manufacturing record would state, ''Vitamin C 250 mg, 1,000,000 tablets'';
- A complete list of components to be used. Again, to continue using the example immediately above, for proposed § 111.45(b)(2), the master manufacturing record also would show that you used starch, microcrystalline cellulose, and dicalcium phosphate in the product;
- An accurate statement of the weight or measure of each component to be used. For example, under proposed § 111.45(b)(3), the master manufacturing record for our hypothetical vitamin C tablet would state the amount of each component used, such as ''200 lbs. of Vitamin C, 10 lbs. of microcrystalline cellulose'' and the amounts of starch and dicalcium phosphate used. (We would not require that you show the amount using an appropriate English or metric standard in a particular way, but we would expect that you use the most appropriate weight or measure for the component);
- The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement in compliance with section 403(s) of the act. For proposed § 111.45(b)(4), therefore, the master manufacturing record for our hypothetical product would state that the dietary ingredient is Vitamin C at 250 mg (because Vitamin C would be the dietary ingredient declared on the Supplement Facts label) and identify starch, microcrystalline cellulose, and dicalcium phosphate (because those ingredients would be in the product's ingredient list, but not on the Supplement Facts label); and
- A statement that explains any intentional excess amount of a dietary ingredient. We recognize that some manufacturers intentionally add a specific amount of a dietary ingredient in excess of the declared label amount so that the finished product can meet the label declaration for that dietary ingredient throughout the product's shelf life. For our hypothetical vitamin C tablet, if you added an extra 25 mg of vitamin C to ensure that your product contains at least 250 mg of vitamin C throughout its shelf life, your master manufacturing record would state the component and the actual amount of the component as ''Vitamin C, 250 mg, (10 percent excess) 25 mg'' or ''275 mg of Vitamin C.'' So, proposed § 111.45(b)(5) would require the master manufacturing record to specify the controlled amount of the excess dietary ingredient necessary to achieve the declared label declaration. This provision is not intended to allow a manufacturer to add excess dietary ingredients in unspecified amounts that would be in excess of the amount actually needed to meet the label declaration.

The agency considered whether to propose requirements in this proposed rule for expiration dating, shelf-life dating, or best if used by dating (hereinafter referred to as expiration dating). Although we recognize that there are current and generally available methods to determine the expiration date of some dietary ingredients, for example vitamin C, we are uncertain whether there are current and generally available methods to determine the expiration dating of other dietary ingredients, especially botanical dietary ingredients. We are not proposing expiration dating at this time because we have insufficient scientific information to determine the biological

activity of certain dietary ingredients used in dietary supplements, and such information would be necessary to determine an expiration date. Further, because official validated testing methods (*i.e.*, AOAC or FDA) for dietary supplements are evolving, especially for botanical dietary ingredients, few official methods are available to assess the strength of a dietary ingredient in a dietary supplement. Nevertheless, if you use an expiration date on a product, you should have data to support that date. You should have a written testing program designed to assess the stability characteristics of the dietary supplement, and you should use the results of the stability testing to determine appropriate storage conditions and expiration dates.

We invite comment on whether any final dietary ingredient and dietary supplement CGMP rule should contain provisions regarding expiration dating and the feasibility of conducting tests needed to support such dates. We also invite comments on whether to require expiration dating on certain dietary ingredients and not others, for example, require expiration dating of vitamin, mineral, and amino acid, but not of botanical dietary ingredients.

Proposed § 111.45(b) also would require your master manufacturing record to contain:

- A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at each point, step, or stage of the manufacturing process where control is necessary to prevent adulteration, and the expected yield when you finish manufacturing the dietary ingredient or dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is performed and material review is conducted and disposition decision is made. In this particular instance, when we refer to the manufacture of dietary ingredients, we mean to say that if you use a master manufacturing record to make dietary ingredients (that is, you make dietary ingredients rather than dietary supplements), the proposal would require the master manufacturing record to contain a theoretical yield at each point, step, or stage where control is necessary to prevent adulteration. Likewise, if you manufacture dietary supplements, the proposal would require your master manufacturing record to contain a theoretical yield at each point, step, or stage where control is necessary to prevent adulteration;
- A description of packaging and a copy of the label to be used. We propose to require such information because, depending on the type of material you use, packaging could adulterate your dietary ingredients or dietary supplements. For example, the correct container may protect the dietary ingredient or dietary supplement from the deteriorating effects of light and if an incorrect container is used that does not provide this protection, your dietary ingredient or dietary supplement could deteriorate and could be adulterated. The description might consist of information such as the type of bottle to be used with your manufacturer's code number, if available; a description of the cap to be used with the liner specified with a manufacturer's code number, if applicable; additional materials needed in packaging; and the control number, if applicable, of the label to be used in packaging the dietary ingredient or dietary supplement. We are not aware of evidence of that dietary supplement manufacturers are using unlawful containers. Section 201(s) of the act defines ''food additive'' to mean any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in it's becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use). Materials used in packaging that come in contact with food or that react chemically with food, may be considered to be food contact substances or food additives. Foods and dietary ingredients may contain active substances that can react with packaging materials. Thus, FDA is proposing a CGMP requirement that manufacturer's use containers that are lawful under the act and that do not impose a risk such as leakage or the possibility of physical contamination of dietary ingredients or dietary supplements. Information on packaging and labels materials will also be helpful in case an adverse event occurs; and
- Written instructions including, but not limited to:

1. Specifications for each point, step, or stage in manufacturing the dietary ingredient or dietary supplement necessary to prevent adulteration;
2. Sampling and testing procedures;
3. Specific actions necessary to perform and verify points, steps, or stages, necessary to meet specifications and otherwise prevent adulteration, including, but not limited to, one person weighing or measuring a component and another person verifying the weight or measure and one person adding the component and another person verifying the addition;
4. Special notations and precautions to be followed; and
5. Corrective action plans for use when a specification is not met.

You should think of the written instructions as being similar to a recipe; they should cover the important steps in your manufacturing, packaging, or holding processes, but they also should tell the reader about any special directions to follow, tests to perform, precautions to be observed, and personnel to use.

Proposed § 111.45(c) would require that you have your quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record. This provision reiterates the quality control requirements in proposed § 111.37. This proposed requirement is necessary to prevent potential problems that could result from changes to the master manufacturing record made by persons who are not qualified to assess the impact of such changes. By having your quality control unit review and approve the master manufacturing record and changes to that record, you will reduce your risk of not detecting the inclusion of an incorrect ingredient in the batch production. The quality control unit review will ensure that necessary inprocess verifications and testing instructions are included in the master manufacturing record. Further, any changes to the master manufacturing record will reduce your risk of adding the wrong component, dietary ingredient or dietary supplement or the wrong amount of a component, dietary ingredient or dietary supplement. For example, in one case, a dietary supplement manufacturer made a product that had 10 times the labeled amount of vitamin D, but did not perform any tests for vitamin D concentration as part of its review of its batch records (Ref. 23). The manufacturer discovered the superpotent batches only after State authorities had contacted them, and had to recall the product. Had the manufacturer's quality control unit reviewed the master manufacturing and batch production records earlier, the superpotent batches that represented a change from the master manufacturing record might have been detected before the product left the manufacturer, and the recall could have been avoided. The manufacturer later took steps to increase its audits of batch records, to require approval of all changes to its master

formulas, and to perform tests for its manufacturing activities.

In another example, several consumers and employees at spas in Massachusetts and Arizona complained of dizziness, vomiting, or lightheadedness after consuming several dietary supplements. We did an inspection and found that, in the case of two products, the manufacturer's formula called for the use of a product having 0.2 percent selenium by weight, but the manufacturer's records showed that it used a product that had 5 percent selenium by weight. This difference meant that the supplements, instead of containing 200 µg of selenium, contained between 400 to 4,699 µg of selenium. After further investigation, we determined that the error occurred when the quantity of selenium to be used was printed in kilograms (kg), instead of g. The change in unit measurement represents a change from the master manufacturing record. Had the manufacturer's quality control unit reviewed the change in the master manufacturing record, it probably would not have approved the change to include use of the product containing the higher percent of selenium.

One comment to the ANPRM opposed a requirement that would have a quality control unit review and approve the master manufacturing record. The comment stated that this review and approval process is overly restrictive because other units can perform this function and only need be audited or periodically verified by the quality control unit. The comment suggested that the quality control unit assure that a master production and control record must be prepared for the manufacture of each dietary ingredient and dietary supplement, rather than review and approve such records.

We do not agree that the review and approval process is overly restrictive and decline to adopt the comment's suggestion. The quality control unit can be composed of individuals from various parts of the organization. Removing this responsibility from the quality control unit would diminish the quality control unit's responsibility and authority. As stated earlier, the manufacturing process of a dietary ingredient or a dietary supplement can be a sophisticated process, and we understand that all organizational units that are involved in critical formulation and manufacturing steps, such as production, engineering, research, and regulatory affairs, should review and approve a master production order and changes to it. However, the responsibility for reviewing and approving the master manufacturing record and modifications to that record properly rests with the quality control unit because the individuals in the quality control unit would have the expertise to make a decision whether the master manufacturing record, if followed, will result in an unadulterated dietary ingredient or dietary supplement and does not mean that the manufacturer needs a large number of employees.

You should note that, while the quality control unit is responsible for reviewing and approving the master manufacturing record and changes to that record, this does not mean that the quality control unit must prepare the master manufacturing record itself or act without any involvement from other parts of your manufacturing operation. Other individuals or groups may help prepare, review, and approve drafts of a master manufacturing record and draft changes to an existing master manufacturing record, but the quality control unit is responsible for reviewing and approving the final master manufacturing record and modifications to that record.

Proposed § 111.45(d) would pertain to written documentation and recordkeeping. Proposed § 111.45(d) would require that you keep your master manufacturing records in accordance with proposed § 111.125. The master manufacturing record in addition to the batch production records will ensure that a complete history of each batch of dietary ingredient or dietary supplement is available for your review in the event that a problem arises with a particular batch. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures.

We invite comment on whether a written procedure for preparing the master manufacturing record and making any modifications to the record, consistent with the requirements in this section, 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. 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.

5. What Requirements Apply to Establishing a Batch Production Record? (Proposed § 111.50)

Proposed § 111.50(a) would require that you prepare a batch production record every time you manufacture a batch of dietary ingredient or dietary supplement. This requirement would apply to any batch, including a batch approved for reprocessing by the quality control unit. The proposal also would require the batch production record to include complete information relating to the production and control of each batch. The batch production record is necessary to document that you followed the master manufacturing record to make each batch of dietary ingredients or dietary supplements. It is important to document such information for each batch because it serves as a check that the master manufacturing record was followed. If you later discover problems with a particular batch of dietary ingredients or dietary supplements, you could look at the batch production record for that batch, compare it to the master manufacturing record, and see whether the problems occurred because of a failure to follow the master manufacturing record. These records, in conjunction with your master manufacturing records, will create a written system which, when followed, will result in a reproducible, high-quality, and uniform dietary ingredient or dietary supplement.

Proposed § 111.50(b) would require the batch production record to accurately follow the appropriate master manufacturing record and also require that you perform each step in producing the batch. Even if you have someone else (such as a contractor) perform a particular step, you would remain responsible for ensuring that each step is done that complies with the

requirements in proposed part 111. The contractor, however, is also considered a manufacturer and must comply with the regulations that apply to the responsibilities that it has specifically contracted to perform.

Proposed § 111.50(c) would specify the batch production record's contents. The proposal would require that certain information be included in the batch production record including, but not be limited to, the following information:

- The batch, lot, or control number;
- Documentation, at the time of performance, showing the date on which each step of the master manufacturing record was performed, and the initials of the persons performing each step including, but not limited to, the person responsible for weighing or measuring each component used in the batch and the person responsible for adding the components to the batch;
- The identity of equipment and processing lines used in producing the batch;
- The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch;
- The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;
- The identity and weight or measure of each component used;
- The initials at the time of performance or at the completion of the batch of the person responsible for verifying the weight or measure of each component used in the batch;
- The initials at the time of performance or at the completion of the batch of the person responsible for verifying the addition of components to the batch;
- A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
- The actual test results for any testing performed during the batch production in accordance with § 111.35(m);
- Documentation that the dietary ingredient and dietary supplement meets specifications;
- Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;
- Any documented material review and disposition decision in accordance with § 111.35(j); and
- The signature of the quality control unit to document batch production record review and any approval for reprocessing or repackaging.

Proposed § 111.50(b) and (c) are necessary to ensure that you made your batches correctly under the master manufacturing record and that you correctly performed each significant step in the manufacturing process. If you did not create a batch production record for each batch production that accurately followed the master manufacturing record, you would not be sure that your dietary ingredient or dietary supplement was not adulterated. The master manufacturing record is intended to ensure batch to batch uniformity and to prevent adulteration. Your batch production record also may be valuable in the event of a product recall. 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.

In one case (Ref. 27), we found that a manufacturer had produced a subpotent folic acid product. When the manufacturer reviewed the batch production records, it discovered that the bulk product was not mixed properly, and this caused the folic acid to be distributed poorly throughout the product. Thus, in this instance, the batch production record helped identify the point in the manufacturing process when the error occurred, and the reason why the error occurred and enabled the manufacturer to correct the problem.

Review of batch production records might have prevented another incident where several persons experienced dizziness, vomiting, or lightheadedness after consuming vitamin and mineral products. As we mentioned in our discussion of proposed § 111.45, this incident involved a mixup during the manufacturing process where the manufacturer's master manufacturing record called for the use of a product having 0.2 percent selenium by weight, but the manufacturer's batch records showed that it used a product that had 5 percent selenium by weight. This difference meant that the supplements, instead of containing 200 µg of selenium, contained between 400 to 4,699 µg of selenium. As discussed earlier, the quality control unit review and approval of the master manufacturing record would have noted the change in percent selenium by weight and the necessary changes to the master manufacturing record could have been made. The quality control unit review and approval of the batch production record provides another check to ensure that a mixup has not occurred. Had the manufacturer's quality control unit compared the master manufacturing record to the batch production record, it would have noticed the mixup during the manufacturing process and prevented the use of the higher percentage selenium dietary ingredient. The information that would be required under proposed § 111.50(c) would help you determine what product was manufactured, when it was manufactured, how it was manufactured, and where it was manufactured. As another example, if your batch production records identify the equipment and processing lines being used, you would be able to go to that piece of equipment or to that processing line and determine which dietary ingredient or dietary supplement is being manufactured or processed. Further, if your batch records reflect the initials of those persons who weighed a component, added that specific component, and performed a particular step to prevent adulteration of the product, you would be able to see who was responsible for a particular action and, if necessary, to consult that person in the event of a problem or to see how he or she performed a particular task. In addition, if your batch production records contain batch or lot numbers and if you later discover a problem with a particular batch, that information will help you investigate the problem by showing you the manufacturing history for that particular batch.

A comment to the ANPRM stated that keeping written records of equipment cleaning and use, including the date, product, and lot number of each batch processed, would be burdensome compared to the benefits it would provide, particularly when equipment is cleaned after each use. The comment added that manufacturers can modify their production records to note which machines they used.

We disagree with the comment. Written records will help you to ensure that all cleaning operations are performed correctly and, if problems do occur with the production of a product, will help you determine whether those

problems are associated with maintenance, cleaning, or sanitizing operations. Batch and lot information, as we stated earlier, will let you identify batches or lots that may have been affected by any equipment or utensil that was improperly maintained, cleaned, or sanitized.

Proposed § 111.50(d) and (e) would set forth your quality control unit's responsibilities regarding batch production records. These responsibilities relate to not only the review but the documentation of their review and decisions about whether a batch could be reprocessed. As we noted in our discussion of proposed § 111.37, the quality control unit has special knowledge and expertise to determine if a batch is produced correctly, that those records are complete, and that it is appropriate to reprocess a batch. The quality control unit also serves as a quality control check that the batch production record accurately follows the master manufacturing record. A quality control unit review of batch production records could have detected and corrected the previously discussed manufacturing error caused by use of the dietary ingredient with the incorrect selenium. Therefore, the review and documentation by the quality control unit of batch production records provides the necessary quality assurance to prevent the production of an adulterated dietary ingredient or dietary supplement.

Specifically, proposed § 111.50(d) would require your quality control unit to review in accordance with § 111.37(b)(5) the batch production record. If a batch production record deviates from the master manufacturing record, including any deviation from specifications, proposed § 111.50(d)(1) would require your quality control unit to conduct a material review and make a disposition decision and record any decision in the batch production record. Proposed § 111.50(d)(2) would instruct your quality control unit to not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.

Proposed § 111.50(e) would require your quality control unit to document in accordance with § 111.37(c) the review performed in accordance with proposed § 111.50(d). The proposal would require the quality control unit to document this review at the time it does the review and would require the review and documentation to include, but would not limit them to, the following:

- Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results;
- Identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master manufacturing record;
- Records of investigations, conclusions, and corrective actions performed in accordance with proposed § 111.50(d); and
- The identity of the person qualified by training and experience who performed the investigation in accordance with proposed § 111.50(d).

Proposed § 111.50(f) would prohibit you from reprocessing a batch that deviates from the master manufacturing record unless your quality control unit approves it for reprocessing. Proposed § 111.50(f) also would prohibit you from reprocessing a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals because you cannot rely on reprocessing to correct public health concerns that a product with pathogens and/or heavy metals would present.

Proposed § 111.50(g) would require that you meet all specifications established in the master manufacturing record for any batch of dietary ingredient or dietary supplement that is reprocessed and would require your quality control unit to evaluate and approve the batch before releasing for distribution. This requirement is intended to ensure that a reprocessed batch is not subject to any lesser specifications than are otherwise applicable to a nonreprocessed batch. Proposed § 111.50(g) also would require that you document the results of the quality control unit's reevaluation in the batch production record.

Proposed § 111.50(h) would require that you collect representative reserve samples of each batch of dietary ingredient or dietary supplement and to keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine whether, for example, the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. Reserve samples also may prove helpful in investigating possible tampering or counterfeiting of your products. We invite comment on whether we should require, in a final rule, that you identify each reserve sample with the batch number so that you can readily identify the correct reserve sample in the event that there is a problem with a particular batch.

Proposed § 111.50(i) would require that you keep your batch production records in accordance with proposed § 111.125. The batch production records in addition to the master manufacturing records will ensure that a complete history of each batch of dietary ingredient or dietary supplement is available for your review in the event that a problem arises with a particular batch. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures.

6. What Requirements Apply to Laboratory Operations? (Proposed § 111.60)

Proposed § 111.60 would establish various requirements for laboratory operations. Proposed § 111.60(a) would require that you use adequate laboratory facilities to perform any necessary tests or examinations to determine that components, dietary ingredients, and dietary supplements you receive meet specifications; that specifications are met during inprocess as specified in the master manufacturing record; and that the dietary ingredients and dietary supplements you manufacture meet their specifications.

One comment to the ANPRM recommended that the regulations related to laboratory operations apply to laboratory facilities located and operated within a company and those facilities that a company may contract with that are located elsewhere. Proposed § 111.60(a) would apply to laboratory facilities generally and is not restricted to laboratory facilities located and operated within a company. In other words, even if you hire a private laboratory to perform various tests for you, proposed § 111.60(a) would require that you make sure that the private laboratory's facilities are adequate to perform whatever tests are necessary. The most important point in proposed § 111.60(a), however, is not where the facility is located, but whether the laboratory facility is adequate for the tests and examinations that need to be done.

Proposed § 111.60(b)(1) would require that you establish and follow laboratory control processes that the quality control unit has approved. For example, under proposed § 111.60(b)(1)(i) and (b)(1)(ii), the laboratory control processes would include use of criteria for selecting appropriate testing and examination methods and for establishing appropriate specifications. Specifications play an important role in CGMP's because they may help

determine whether a dietary ingredient or dietary supplement is adulterated.

Criteria for establishing appropriate specifications must be specific to the component, dietary ingredient, or dietary supplement. The specifications are the parameters that you must meet. For example, for ascorbic acid, your specifications would include all the criteria that you want your incoming dietary ingredient or for your finished product to meet. For example, you might establish criteria for the appearance, color, odor, identity using one or more tests, heavy metals (*e.g.*, lead, arsenic, mercury), and organic volatile impurities.

Similarly, criteria for selecting appropriate test and examination methods include parameters such as type of tests and examinations needed based on the component you receive. For example, you might use morphological characters and organoleptic characteristics in some cases to identify botanical dietary ingredients at the time of collection or for unprocessed botanicals. When sufficient morphological characters are present to separate the plant species from other plant species, an accurate identification can be made since morphological characters are the sole basis of distinguishing most of the world's plant species. However, unprocessed botanicals that do not contain all the plant parts necessary to include adequate morphological characters to assure the correct species should have other identity aids or tests to assure the identity of the botanical. It is possible to use only a picture as an identity standard for whole fresh Ginkgo leaf from a cultivated field because the Ginkgo leaf is not easily confused with the leaf shape, venation, and color of other leaves that could be present in the field. In contrast, powdered Ginkgo leaf is a different form of the dietary ingredient and would require microscopic and/or chemical analysis. Ginkgo extracts have no morphological or anatomical features, and it is possible that extracts may include a number of chemical compounds at different ratios and concentrations that would require a different chemical test to assure the identity of the dietary ingredient. Botanical dietary ingredients that come from wild rather than cultivated sources may grow among and be unintentionally harvested with ''poisonous'' plants; therefore, an identity test also would need to show whether a botanical dietary ingredient is adulterated with another substance or a poisonous plant.

To illustrate this point, a specification may contain a simple identity test, and these tests may show whether a dietary ingredient is adulterated with another substance or is a poisonous plant that should not be ingested. Misidentification or a mixup of botanical ingredients can cause a product to be adulterated (Refs. 6 and 69 through 73). Heavy metals may contaminate botanical and natural-occurring ingredients if a plant is grown and harvested in an area contaminated with heavy metals or even processed in a contaminated area (Refs. 74 and 75). Pesticides also may contaminate botanical ingredients; this occurs in rural areas where the botanical plant grow alongside commercial crops (Ref. 64). Therefore, you must consider what criteria you need to include for the types of testing that are needed, for example, for heavy metal or pesticide contamination, or identity testing criteria for selecting appropriate test methods, for example, whether to use organoleptic or chemical analyses for identity testing. In addition, you must establish criteria for specifications for the tests and examinations used. Establishing such criteria for specifications and appropriate test and examination methods will provide you with internal processes that will help prevent misidentification and contamination.

Proposed § 111.60(b)(1)(iii) would require your laboratory control processes to include use of sampling plans for obtaining representative samples of:

- Components, dietary ingredients, and dietary supplements received;
- Inprocess materials during the batch manufacturing when testing or examination is required in the master manufacturing record;
- Each batch of dietary ingredient or dietary supplement manufactured to determine that the dietary ingredient or dietary supplement meets specifications;
- Packaging and labels received to determine that the materials meet specifications; and
- Each batch of packaged and labeled dietary ingredients or dietary supplements to ensure that the label specified in the master manufacturing record has been applied.

For example, a representative sample is important to being able to have an adequate sample to detect contamination. Contamination may not be distributed evenly throughout a product and may not be detected without a representative number of units. Determining the size of a representative sample is important because the sample size must be large enough to meet your testing needs for specific types of components, dietary ingredients, or dietary supplements, and packaging and labels. Your sampling plans should include reserve samples, too, because reserve samples will enable you to investigate and identify possible manufacturing problems in the future. The proposal would not specify any particular sampling plan; it would leave such details to your discretion so that you can develop a sampling plan that suits your products and your testing needs.

Proposed § 111.60(b)(iv) through (b)(vi) would require the laboratory control processes to include:

- Use of criteria for selecting standard reference materials used in performing tests and examinations. An authenticated plant reference material may be used as standard reference material in performing certain organoleptic examinations. An authenticated plant reference material is material that has been authenticated as the correct plant species and correct plant part(s) by a qualified plant taxonomist. As described earlier in this document, an organoleptic examination may be an appropriate examination to confirm plant identity when sufficient morphological characters are present to separate the plant species from other plant species. For microscopic and chemical tests, a reference material is a highly purified compound that is well characterized, and you would use the reference material to perform tests including calibration tests. In general, there are two types of reference materials: (1) Compendial reference standards that do not require characterization; and (2) noncompendial standards. Noncompendial standards should be of the highest purity that can be obtained by reasonable effort and should be thoroughly characterized to assure their identity, purity, quality, and strength. Ideally, you should use compendial reference standards whenever possible, but if no compendial reference standard exists, you should establish appropriately characterized inhouse materials prepared from representative lots;
- Use of appropriate test method validations. Test method validation determines whether a newly-developed or existing test method is accurate, precise, and specific for its intended purpose. We have discussed previously the terms ''accurate'' and ''precise.'' Validation involves evaluating the test method on multiple occasions or in multiple test facilities. Official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions. The AOAC International methods that are validated

in collaborative studies often are often cited as ''official validated methods.'' If you modify an officially validated method, you should document the reason for the modification and have data to show that the modified method produced results that are at least as accurate and reliable as the established method for material being tested. Further, you should have complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions that you use in your laboratory operations. Proposed § 111.25(b)(1) would require calibration of laboratory instruments, apparatus, gauges, and recording devices. Validated methods also exist in official compendia for vitamins, minerals, and several botanicals, so you should use validated methods whenever available. You may use validated methods that can be found in official references, such as AOAC International, USP and others. Other method validations are conducted using two or three laboratories or in a single laboratory by repeating the same test multiple times. Official and nonofficial method validations use similar performance parameters in conducting method validations. If an official validated method does not exist in an official reference, the method you use may be validated by using multiple tests at your laboratory or multiple laboratories performing the same test to document that the intended use of the method is consistently fulfilled. You must validate that the official or nonofficial method works under your conditions of use in your setting. You also should conduct day-to-day validations of the method that you use, whether it is an official validated method or a less-formal validated method, under the conditions of use to ensure that the method will provide the information you need to ensure that your dietary ingredient or dietary supplement has the identity, purity, quality, strength, and composition that it is supposed to have and is thus not adulterated. Consistent, day-to-day test recoveries for the reference material are one indicator that the analytical method is working. There are at least two references that describe test method validation performance parameters: (1) Performance parameters for chromatographic methods are described in ''Reviewer Guidance, Validation of Chromatographic Methods'' (Center for Drug Evaluation and Research, FDA, November 1994) (Ref. 76); and (2) International Conference on Harmonisation (ICH); Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (63 FR 31506, June 9, 1998); and

- Use of test methods in accordance with established criteria. Your process for performing test methods criteria must include sufficient detail, including the material you are testing, the purpose of the test, and the test method. The description of the test method criteria must include any reagents used and preparation instructions, apparatus required, any instructions for preparing the sample to be tested, and instructions for conducting the examination. For example, if you receive components of plant origin from an outside source, your specifications must indicate that you test those components to verify that they are not contaminated with adulterants of vegetable origin and to determine that the microscopic examination method is appropriate for use. Further, you may decide that the AOAC International Official Method 961.01 entitled ''Adulterants in Spices'' is the appropriate analytical method to detect the contaminant which is a method to detect adulterants of vegetable origin in spices. Your test methods criteria must specify the component, dietary ingredient, or dietary supplement to be tested, and what specifically to test for, *e.g.*, the identity of the component, dietary ingredient, or dietary supplement, or a specific contaminant. The method criteria must provide detailed information about performing the analysis (*i.e.*, the reagent solutions needed and their preparation, the type of microscope and other equipment required, preparing the sample, and examination instructions). The proposed rule would not require that you test for any specific substance and would not require a specific test for a substance, so you would be able to evaluate what the most appropriate test would be for the component, dietary ingredient, or dietary supplement and to use the test methods that are suited to your products and your manufacturing needs. Your test methodology must be specific for the component, dietary ingredient, or dietary supplement and the specifications you have established.

Proposed § 111.60(b)(2) and (b)(3) would apply to documentation and recordkeeping for your laboratory operations. Proposed § 111.60(b)(2) would require the person who conducts the testing and examination to document, at the time of performance, that they followed the laboratory method and the testing and examination results. Proposed § 111.60(b)(3) would require that you keep laboratory testing and examination records in accordance with proposed § 111.125. Laboratory records are necessary to ensure compliance with established specifications and to demonstrate compliance with the CGMP and quality control processes.

Proposed § 111.60(c) would require that you verify that the laboratory testing methodologies are appropriate for their intended use.

Proposed § 111.60(d) would require that you identify and use the appropriate validated testing method to use for each established specification for which testing is required to determine whether the specification is met. In other words, the proposal would recognize that requiring that you have testing methods is not sufficient alone; you must also use those testing methods to prevent the adulteration of dietary ingredients or dietary supplements.

We invite comment on whether we should require, in a final rule, written procedures for your laboratory operations and should require that the person who performs the laboratory processes document, at the time of performance, that the laboratory processes were performed. 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.

7. What Requirements Apply to Manufacturing Operations? (Proposed § 111.65)

Proposed § 111.65 would require that you take all necessary precautions to ensure that, during the manufacturing operations, you do not create a source of possible contamination and that specifications are consistently achieved.

Under proposed § 111.65(a), you must design or select equipment and processes to ensure that dietary ingredient or dietary supplement specifications are consistently achieved. Frequently, a computer or system of computers may control many or all stages of manufacturing operations such as mixing, producing tablets, and packaging. It is important that such systems and equipment function as expected to ensure that the dietary ingredient or dietary supplement contains a homogenous mixture, a tablet that is neither too hard or too friable, and that the packaging contains the correct dietary ingredient or dietary supplement. Equipment used in dietary ingredient or dietary supplement manufacture, packaging, and label operations must be, for example, of an appropriate size and installed properly in order to produce an unadulterated product. If not designed or installed properly, the equipment can result in a variety of problems. For example, a mixer for the blending of powdered ingredients will not properly perform its function if the blade is too small relative to the size of the mixer or not properly placed inside of the mixer. Such a mixer may produce an adulterated product because the dietary supplement, for example, is not of uniform composition and therefore would not be able to meet the specifications for purity, quality, strength, or composition in the final product. Thus, equipment design and selection is critical to ensure that you manufacture an unadulterated dietary ingredient or dietary supplement.

Proposed § 111.65(b) would require that you conduct all manufacturing operations in accordance with adequate sanitation principles. We discussed the importance of having adequate sanitation earlier and related it to the use of sanitary practices for employees, physical plant, and equipment.

Proposed § 111.65(c)(1) through (c)(11) would require that you take all the necessary precautions during the manufacture of dietary ingredients and dietary supplements to prevent contamination of components, dietary ingredients, and dietary supplements.

Proposed § 111.65(c)(1) would require that you perform manufacturing operations under conditions and controls that protect against the potential for microorganism growth and the potential for contamination. This would require that you conduct all operations in receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, sorting, and packing dietary ingredients and dietary supplements in accordance with appropriate and established sanitation procedures. Operations with poor sanitation in the production and processing environment can significantly increase the risk of contaminating components, dietary ingredients, or dietary supplements. Pathogenic microorganisms may be found on the floors and in the drains of the processing area and on all contact surfaces. Without good sanitary practices, any surface that comes in contact with components, dietary ingredients, and dietary supplements could be a potential source of microbial contamination. Thus, using appropriate sanitation procedures would provide conditions and controls to protect against potential contamination and microbial growth.

Proposed § 111.65(c)(2) would require that you wash or clean components that contain soil or other contaminants. This is a basic sanitation procedure to protect against contamination and microbial growth. Raw agricultural materials and other components that contain soil or other contaminants must be washed or cleaned as necessary. Water quality used for washing, rinsing, or conveying raw agricultural materials must be adequate for its intended use, both at the start and at the end of the processing operation, and should not contribute to the contamination of such materials.

Proposed § 111.65(c)(3) would require that you use water that meets the EPA's NPDW regulations or, where necessary, higher sanitary quality and that complies with all applicable Federal, State, and local regulations for water that is used in the manufacturing operation. If you reuse water that was used to remove soil or contaminants from components, the proposal would require that the reused water be safe and of adequate sanitary quality so that it does not become a source of contamination. Some manufacturing operations may require water of a higher sanitary quality than water that meets the NPDW regulations. For example, the fluoride or chloride levels in water meeting the NPDW regulations may interfere with certain capsule or tablet operations and a higher quality water such as distilled water may be necessary. This proposed requirement allows the manufacturer discretion in determining whether NPDW regulations or higher sanitary quality water is necessary for a manufacturing operation.

Proposed § 111.65(c)(4) would require that you perform chemical, microbiological, or other testing, as necessary, to prevent the use of contaminated components, dietary ingredients, and dietary supplements. You should consider identifying those areas in the processing and production areas where chemical, microbial, or other forms of contamination are most likely to occur. Chemical, microbial, or other testing is necessary to identify areas where sanitation measures have not been adequate or where products may become adulterated.

Proposed § 111.65(c)(5) 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. The measures you decide to use to remove, destroy or prevent the growth of microorganisms on or in your components, dietary ingredients, or dietary supplements must be appropriate under the conditions of manufacture, handling, and distribution. Such measures are necessary to prevent their adulteration and misbranding. Microorganisms include pathogenic bacteria that, if present would adulterate the product. In addition, decomposition may result in a change in the component, dietary ingredient, or dietary supplement strength; the consequence of not using the appropriate measure may be that the dietary ingredient or dietary supplement no longer meets specifications, and thus, would be adulterated under section 402(g) of the act and misbranded under section 403 of the act. By including the phrase, ''any other effective means,'' we provide you with discretion to decide which measures to use to destroy or prevent the growth of microorganisms and to prevent decomposition.

Proposed § 111.65(c)(6) would require that you hold components, dietary ingredients, and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents them from becoming adulterated.

Proposed § 111.65(c)(7) would require that you identify and hold any components, dietary ingredients, and dietary supplements, that require a material review and disposition decision, in a manner that protects the components, dietary ingredients, and dietary supplements against

contamination and mixups. A dietary ingredient or dietary supplement under this proposed rule would require a material review and disposition decision when the components, dietary ingredients, or dietary supplements deviate from specifications. As previously explained, the specifications established as production and process controls under proposed subpart E of part 111, are regulatory specifications. Thus, a deviation from such a specification means that the components, dietary ingredients, or dietary supplements may be adulterated. Any component, dietary ingredient, or dietary supplement that may be adulterated must be segregated from such material that meets specifications so that it does not become a source of contamination. The proposal would require that you hold these components, dietary ingredients, and dietary supplements in a manner that protects against contamination and mixups.

Proposed § 111.65(c)(8) would require that you perform mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary ingredients or dietary supplements against contamination. Such steps must include consideration of cleaning and sanitizing contact surfaces, using temperature controls, and using time controls. For example, when blending components, if you use a mixer that has not been cleaned and sanitized, your blended material may become contaminated with microorganisms, including microbial pathogens. Thus, it is important to clean and sanitize your mixer before use.

Proposed § 111.65(c)(9) would require that you use effective measures, such as filters, traps, magnets, or electronic metal detectors, to protect against the inclusion of metal or other foreign material in your components, dietary ingredients, or dietary supplements. This proposed requirement is intended to exclude foreign and extraneous matter that would contaminate components, dietary ingredients, or dietary supplements. The purpose of this proposed requirement is not to exclude dietary ingredients that are intended to be used and that are of mineral origin.

One comment to the ANPRM suggested that we require the use of effective measures to protect against the inclusion of metal or other extraneous material in dietary products when there is reason to suspect that the product is contaminated by metal or other extraneous material. The comment stated that manufacturers typically are able to identify the particular piece of equipment that is the source of the metal contamination.

We disagree with the comment. The purpose behind proposed § 111.65(c)(9) is to ensure that no metal or foreign material becomes a source of possible contamination and not to establish mechanisms to be used after contamination has or is suspected to have occurred. We believe that the most practical way to protect against the inclusion of metal and foreign material is to require that you use effective measures during the manufacturing operations. The source of metal contamination is not limited to equipment and we previously emphasize the need to maintain equipment to prevent such contamination. Metal contamination also may occur during harvesting of natural products and use of utensils such as metal brushes. Therefore, because we believe that it is not possible to identify and eliminate all possible sources of metal contamination or to determine when measures would be necessary to eliminate such contamination, proposed § 111.65(c)(9) would require that you use effective measures to protect against the inclusion of metal and foreign material for all your manufacturing operations.

Proposed § 111.65(c)(10) would require that you segregate and identify all containers for a specific batch of dietary ingredients or dietary supplements to identify their contents and, where necessary, the phase of manufacturing. This proposed requirement is intended to protect ingredients or dietary supplements from potential contamination or misuse during manufacturing or storage. Identifications of these items will enable you to determine accurately the status of all batches of dietary ingredients or dietary supplements during all stages of the manufacturing process, will help to prevent mixups in the addition of components or dietary ingredients to the dietary supplement and will facilitate prompt action if any problems in processing are identified.

Proposed § 111.65(c)(11) would require that you identify all processing lines and major equipment used during manufacturing and to indicate their contents, including the name of the dietary ingredient or dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing. The same reasons given for proposed § 111.65(c)(10) apply to this proposed requirement.

Proposed § 111.65(d) would require that you conduct a material review and make a disposition decision in accordance with proposed § 111.35(i) for any component, dietary ingredient, or dietary supplement that fails to meet specifications or that is, or may be, adulterated. If the material review and disposition decision allows you to reprocess the component, dietary ingredient, or dietary supplement, proposed § 111.65(d) would require that you retest or reexamine it to ensure that it meets specifications and is approved by the quality control unit.

The person who performs the material review and disposition review required in accordance with this section would be required to document at the time of performance the results of the material review and disposition decision. In accordance with § 111.50(d), such documentation must be maintained with the batch production record.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures to implement the manufacturing operations required in proposed § 111.65. 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.

8. What Requirements Apply to Packaging and Label Operations? (Proposed § 111.70)

Proposed § 111.70 would establish requirements for your packaging and label operations. The correct use of packaging and labels can affect whether your product is adulterated. For example, if a packaging material, intended only for use with a dry product, is used to package a liquid, unsafe substances could migrate from the packaging to the liquid, and adulterate your dietary ingredients or dietary supplements. In addition, if you apply the wrong label, your product would be adulterated under section 402(g) of the act because your label must be that which is specified in the master manufacturing record. In addition, your product would be misbranded under section 403 of the act.

Proposed § 111.70(a) would require that you take necessary actions to ensure each packaging container for holding dietary ingredients or dietary supplements meets its specifications so that the packaging container's condition will not contaminate your dietary ingredients or dietary supplements or cause them to deteriorate. As previously stated in the discussion of proposed § 111.35(e)(4), you must establish specifications for packaging materials that may come in contact with dietary ingredients or dietary supplements. Meeting such specifications would ensure that the packaging that is used is safe and suitable for the intended use and meets all of the statutory and regulatory requirements under the act. In that way, the packaging materials will not adulterate the dietary ingredient or dietary supplement. This proposed requirement would give you the discretion to establish the specifications for each packaging container, and would require that these specifications are routinely met. For example, if your product is sensitive to light, you would choose a container that protects the product from the light so that it does not deteriorate.

Proposed § 111.70(b) would require that you fill, assemble, package, and perform other related operations in a way that protects your dietary ingredients or dietary supplements against adulteration and misbranding. The proposal would require that you use any effective means to do this, which would include:

- Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary ingredient or dietary supplement containers, as appropriate. This is important because cleaning and sanitizing all filling and packaging equipment can help you avoid some common mistakes that can adulterate your products. For example, in one case, a consumer complained about receiving two different sized capsules in a bottle labeled as containing acidophilus capsules. We conducted an investigation and found that the manufacturer had received a similar report from a different consumer (Ref. 77). We analyzed the capsules and found that the smaller capsules were not acidophilus capsules but contained levels of stannous fluoride that would cause convulsions in certain persons and even exceeded the lethal dose in small children. We also collected unopened bottles of the acidophilus product and, after opening the product, found different sized capsules. The presence of smaller capsules containing stannous fluoride mixed in with the larger acidophilus capsules adulterated the product. The fact that these small stannous fluroride capsules mixed in with the larger acidophilus capsules indicated that the manufacturer had not cleaned the filling equipment properly.

In another case, consumer complaints about a vitamin C product prompted us and the product's manufacturer to investigate the product (Ref. 78). We both discovered that the products contained niacin instead of vitamin C, and the problem was the result of a failure to clean out the packaging equipment so that niacin that had been left in the packaging equipment was put into the capsules during the manufacturing operation for the vitamin C product. The manufacturer reviewed its packing operations and instructed its personnel at the manufacturing plant to prevent this problem from reoccurring.

- Protecting manufactured dietary ingredients and dietary supplements from contamination, particularly airborne particulates such as dust, dirt, or microbes that may contaminate your product when your product is exposed to the environment.
- Using sanitary handling procedures.
- Establishing physical or spatial separation of packaging and labels from operations on other dietary ingredients and dietary supplements to prevent mixups. It is important to keep inprocess material separate from finished product that is ready to be packaged and labeled so that inprocess material is not inadvertently packaged and labeled as finished product. In addition, this proposed requirement would prevent mixup of one type of dietary ingredient with another type of dietary ingredient during packaging and label operations such as the vitamin C and niacin mixup described earlier.
- Identifying, by any effective means, filled dietary ingredient or dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mixups;
- Identifying the dietary ingredient or dietary supplement with a batch, lot, or control number that can be used to determine the manufacturing history and control of the batch. Using a unique identifier for each batch or lot is necessary for you to trace the manufacturing history for a particular batch, and thus help you investigate and correct any safety problems for a batch or to recall a dietary ingredient or dietary supplement batch. For example, if you discovered a particular batch had a safety problem, you could recall the batch by identifying the batch number for the problem product. If you did not have a unique identifier, consumers would be unable to determine which product was the subject of a recall, and they may not stop using the product or you will have to recall more of the product.
- Examining a representative sample of the packaged and labeled dietary ingredient or dietary supplement to ensure that it meets specifications and that the label specified in the master manufacturing record has been applied; and
- Suitably disposing of labels and other packaging for dietary ingredients or dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and label operations. The use of any obsolete or incorrect label would adulterate the product because it would not comply with the requirement that the correct label as specified in the master manufacturing record be used.

Proposed § 111.70(c) would require that you conduct a material review and make a disposition decision of any packaged and labeled dietary ingredients or dietary supplements that do not meet specifications. If packaged and labeled dietary ingredients or dietary supplements do not meet specifications, it means that there is a problem and that the dietary ingredient or dietary supplement may be or is adulterated and this step is needed to determine what to do and how to handle the product to ensure that it does not get distributed.

Sometimes problems arise because a manufacturer used the wrong label on a particular ingredient. For example, in one case, an ingredient manufacturer put the wrong label on its product so that a product labeled as containing zinc picolinate actually contained zinc polynicotinate (Ref. 79). The dietary

ingredient went to another manufacturer who, believing that the product was zinc picolinate, used the dietary ingredient to make its dietary supplement. The error was discovered after consumers who used the product started complaining of adverse reactions that are associated with niacin supplements, but the problem could have been avoided if the dietary ingredient manufacturer had taken steps to ensure that the correct labels were used.

Proposed § 111.70(d) would require that you repackage or relabel dietary ingredients or dietary supplements if approved and appropriately documented by your quality control unit. The quality control unit would need to decide whether the improperly packaged product was adulterated by the incorrect package and could be repackaged and relabeled without reprocessing of the dietary ingredient or dietary supplement.

Proposed § 111.70(e) would require that you retest or reexamine any repackaged or relabeled dietary ingredients or dietary supplements. They must meet all specifications and the quality control unit must approve or reject their release for distribution. The reason this is necessary is to ensure for example, by testing or examination, that the repackaged or relabeled product meets specifications and that the container in which the product is repackaged meets specifications.

Proposed § 111.70(f)(1) would require that you control the issuance and use of packaging and labels and reconcile the issuance and use of discrepancies. It is important to control access to the storage of packaging and labels; for example, only the labels that are required for current label operations should be issued to prevent issuance of any incorrect labels during the label operation. Using batch or lot numbers on your labels may be one control method. Batch or lot numbers also help you (and us) to identify a particular product and to trace that product's manufacturing history through your CGMP records. They can help identify which products are affected by a product recall, if a recall is necessary, and this can help preserve consumer confidence in your product.

For example, if a recall covers batch A123, and a particular consumer has a product whose batch number is C456, he or she will know that the product is not covered by the recall. In contrast, if no batch numbers appear on the product label, the consumer would not be able to tell whether his or her product is covered by the recall and may continue to use it.

As another example, controlling access of labels can help identify instances when mislabeling may have occurred. If you issue only the necessary number of labels to cover a particular production run but use fewer labels than expected even though you labeled the expected number of containers for the production run, this discrepancy would suggest that you used some wrong labels during the run and that you should conduct an investigation to determine the cause of, or reconcile the discrepancy.

Proposed § 111.70(f)(2) would require that you must examine carefully, before packaging operations, packaging and labels for each batch of dietary ingredient or dietary supplement to ensure that the label and packaging conform to the master manufacturing record.

Proposed § 111.70(g) would require that the person who performs the requirement established in accordance with this section document, at the time of performance, that he or she performed the requirement. This would include, but not be limited to, documentation in the batch production record of:

- The identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use;
- The examination of a representative sample (as proposed § 111.70(b)(7) would require);
- The conclusions you reached from retests conducted under proposed § 111.70(e); and
- Any material reviews and disposition decisions for packaging and labels.

Proposed § 111.70(h) would require that you keep the packaging and label operations records required under this section established in accordance with proposed § 111.125. These records are necessary to ensure that the correct packaging and label, *i.e.*, the packaging and label specified by the master manufacturing record, were used in and applied to the batch of dietary ingredient or dietary supplement. These records together with the master manufacturing records and batch production records will ensure that a complete history of each batch of dietary ingredient or dietary supplement including use of the correct packaging and label is available for your review in the event that a problem arises with a particular batch. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures. We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for packaging and label operations that implement the requirements of this section. 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.

9. What Requirements Apply to Rejected Components, Dietary Ingredients, Dietary Supplements, Packaging, and Labels? (Proposed § 111.74)

Proposed § 111.74 is intended to ensure that you do not mistakenly use rejected materials that are determined by the quality control unit to be unsuitable for use to make a dietary ingredient or dietary supplement.

Proposed § 111.74(a) would require that you clearly identify, hold, and control, under a quarantine system any component, dietary ingredient, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or label operations. The term ''control under a quarantine system'' indicates that you must prevent the use of any rejected component, dietary ingredient, dietary supplement, packaging, or label because such rejected product is unsuitable for use. For example, under this proposed rule, if a component, dietary ingredient, or dietary supplement is rejected and determined by the quality control unit

to be unsuitable for use, such material would be adulterated and not be suitable for reprocessing. Therefore, to prevent contamination of nonrejected material, you must quarantine the rejected material before disposal. The proposed rule would not specify any particular mechanism for how you quarantine the material, instead, you would have discretion in deciding what actions to take or what process to use.

You also should note that, by referring to items that are rejected and unsuitable for use, proposed § 111.74(a) excludes items that can be reprocessed and made suitable for use. Those items that can be reprocessed and made suitable for use are dealt with in proposed § 111.82.

*F. Holding and Distributing (Proposed Subpart F)*

1. What Requirements Apply to Holding Components, Dietary Ingredients, Dietary Supplements, Packaging, and Labels? (Proposed § 111.80)

Proposed § 111.80 would require that you hold dietary ingredients and dietary supplements under conditions that will protect them against contamination and deterioration. Proposed § 111.80(a) would require that you hold components, dietary ingredients, and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, quality, strength, and composition of the components, dietary ingredients, and dietary supplements are not affected. This proposed provision includes the holding of components, dietary ingredients, dietary supplements in your physical plant and at any point in the distribution process, however, we would not extend the holding requirements under this proposed CGMP regulation to retail establishments, but would defer to State and local governments for regulating operations that provide dietary supplements to retail for sale to the consumer. However, if a retail holding area is filthy, we would not be prevented from taking an enforcement action under a legal authority other than section 402(g) of the act.

This requirement would ensure that products are not contaminated while they are held by the manufacturer, the wholesaler, or while being held at a warehouse. This would increase the likelihood that the products consumers purchase have the same quality as when they left the manufacturer. Note that proposed § 111.80(a) uses the words ''not affected;'' this means that the conditions under which you hold components, dietary ingredients, and dietary supplements must not adulterate the components, dietary ingredients, or dietary supplements. For example, dried plants stored in a hot, humid warehouse may become moldy. Mold contamination could adversely affect the purity of the dietary ingredients and dietary supplements you manufacturer. You will decrease the chances of mold contaminating your dried plants if you control temperature and humidity.

Proposed § 111.80(b) would require that you hold packaging and labels under appropriate conditions of temperature, humidity, and light so that the quality of the packaging and labels are not affected. For example, some plastics become brittle when exposed to extreme temperatures. If brittle plastic containers are used to hold dietary ingredients or dietary supplements, they could crack or break, thereby losing their protective qualities, and lead to contamination or deterioration of the dietary ingredient or dietary supplement. You need to know the conditions of temperature, humidity, and light that are appropriate for your packaging and labels and you need to hold the packaging and labels under such conditions.

Proposed § 111.80(c) would require that you hold components, dietary ingredients, dietary supplements, packaging, and labels under conditions that do not lead to mixup, contamination, or deterioration of the components, dietary ingredients, dietary supplements, packaging, and labels. For example, your holding conditions must include a system for identifying container contents and its status (*e.g.*, segregated, approved for use) in a manner that prevents mixup or use of unsuitable materials in manufacturing. Further, the presence of rodents in your holding area may cause contamination or deterioration of components, dietary ingredients, dietary supplements, packaging, and labels. Therefore, your holding conditions must be rodent-free. Moreover, rodents in your holding area would adulterate your dietary ingredient or dietary supplement under section 402(g) of the act. Holding conditions that prevent mixup, contamination, or deterioration of components, dietary ingredients, dietary supplements, packaging, or labels are necessary to prevent the production of an adulterated dietary ingredient or dietary supplement.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for holding components, dietary ingredients, dietary supplements, packaging, and labels. 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.

2. What Requirements Apply to Holding Inprocess Material? (Proposed § 111.82)

Proposed § 111.82 discusses proposed requirements for holding inprocess material. Proposed § 111.82 would require that you segregate any inprocess material that does not meet your specifications, is awaiting further processing, or needs further evaluation by the quality control unit (*e.g.*, because the inprocess material does not meet specifications, or because of an unexpected occurrence) to determine if it is suitable for reprocessing.

Proposed § 111.82(a), therefore, would require that you identify and hold inprocess material under conditions that will protect such material against mixup, contamination, and deterioration.

Proposed § 111.82(b) would require that you hold inprocess material under appropriate conditions of temperature, humidity, and light. The intent here is to prevent any contamination or deterioration of that inprocess material.

We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for holding inprocess material. 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.

3. What Requirements Apply to Holding Reserve Samples of Components, Dietary Ingredients, and Dietary Supplements? (Proposed § 111.83)

Earlier, we discussed a provision concerning the collection of reserve samples. Proposed § 111.50(h) would require that you collect representative reserve samples of each batch of dietary ingredient or dietary supplement. Proposed § 111.83 would set forth requirements for holding any reserve samples collected.

Proposed § 111.83(a) would require that you hold any reserve samples of components or dietary ingredients collected in a manner that protects against contamination and deterioration.

Proposed § 111.83(b) would require that you hold such reserve samples of dietary supplements in a manner that protects against contamination and deterioration. Further, this provision would require that you hold the reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use. This proposed requirement also would require that you use the same container-closure system in which the dietary supplement is marketed or one that provides the same level of protection against contamination or deterioration as the marketed container-closure system. It is necessary to hold the reserve sample of a dietary supplement under the same conditions and in the same packaging as you would expect a consumer to hold that dietary supplement so that, if you need to later test that reserve sample, the testing would reflect current conditions under which the dietary supplement is held by the consumer prior to being consumed.

4. What Requirements Apply to Returned Dietary Ingredients or Dietary Supplements? (Proposed § 111.85)

Proposed § 111.85 would establish requirements for returned dietary ingredients or dietary supplements. ''Returned'' dietary ingredients or dietary supplements are those products that a distributor, wholesaler, or retailer returns to a manufacturer. Proposed § 111.85(a) would require that you identify returned dietary ingredients or dietary supplements and to quarantine them until your quality control unit conducts a material review and makes a disposition decision. (Your quality control unit would do this under proposed § 111.37.) For example, you could attach a tag or other identifier on the returned dietary ingredient or dietary supplement to show that it is ''returned.'' We would require that you identify and quarantine (not just identify and segregate) returned dietary ingredients or dietary supplements so that they cannot be used. We propose to require that you quarantine returned products because you must assume that the returned product is adulterated until tests show otherwise. Thus, the product should not have physical closeness or contact with nonreturned product to ensure that it will not be mixed up mistakenly with nonreturned product, redistributed or reused in manufacturing.

Proposed § 111.85(b)(1) states that you may salvage returned dietary ingredients and dietary supplements only if:

- Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions. This would require that you have personal knowledge of the exact conditions under which the returned dietary ingredients or dietary supplements were held. Normally, for most types of packaging, simply examining the packaging will not tell you about the storage conditions that existed. However, we are aware of some technologies that are being used, such as temperature-sensitive materials that change colors, that could provide some information about storage conditions; and
- Tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition. This requirement will ensure that you do not return to distribution a dietary ingredient or dietary supplement that does not meet specifications. Salvage is available for only those products for which testing can be performed on finished product.

For purposes of this discussion, ''salvage'' means to return to distribution without reprocessing the dietary ingredient or dietary supplement.

Proposed § 111.85(c) would require that you destroy or suitably dispose of the returned dietary ingredients or dietary supplements if they do not meet specifications for identity, purity, quality, strength, and composition, unless the quality control unit conducts a material review and makes a disposition decision to allow reprocessing.

Proposed § 111.85(d) would require that you conduct an investigation of your manufacturing processes and those other batches if the reason for a dietary ingredient or a dietary supplement being returned implicates other batches. The point of the investigation would be to determine whether, for example, the other implicated batches may have the same problem or have been subject to the same problematic manufacturing process for which the dietary ingredient or dietary supplement was returned. Other batches may be implicated if the component or dietary ingredient used in the returned product also was used in additional batches or if your investigation indicates that there was a problem with a step in the manufacturing process that affected additional batches. The proposal also would require that you document the investigation and include your conclusions and followup.

Proposed § 111.85(e) would require you to establish and keep records for any material review and disposition decision and any required testing to determine compliance with specifications done for any returned dietary ingredient or dietary supplement. You should include the following information in your records:

- The name of the person or company or both the name of the person and company who returned the dietary ingredients or dietary supplements;
- A description of the returned dietary ingredient or dietary supplement;
- The batch or lot number of the returned dietary ingredient or dietary supplement and any reprocessed batch or batch manufactured using the returned dietary ingredient or dietary supplement;
- The reason for the return;
- The quantity returned;
- The disposition of the dietary ingredient or dietary supplement; and
- The date of disposition.

Proposed § 111.85(f) would require that you make and keep records for returned dietary ingredients and dietary supplements in accordance with § 111.125. These records are necessary to ensure that returned products that could be adulterated are not inadvertently redistributed or inadvertently used in manufacturing. Further, records of any reprocessed batch or batch manufactured using the returned product will be useful in the event that a problem arises with a particular batch that is manufactured with returned product. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures. We invite comment on whether we should require, in a final rule, that you establish and follow

written procedures for identifying, quarantining, and salvaging returned dietary ingredients and dietary supplements. 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.

5. What Requirements Apply to Distributing Dietary Ingredients or Dietary Supplements? (Proposed § 111.90)

Proposed § 111.90 would establish requirements concerning the distribution of dietary ingredients and dietary supplements. Proposed § 111.90(a) would require any distribution of dietary ingredients or dietary supplements to be under conditions that will protect them from contamination and deterioration. This is to protect dietary ingredients and dietary supplements from distribution practices that may adulterate them.

As discussed previously, 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. It also would apply to persons who distribute 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) of the act.

We recognize that the safety of dietary supplements cannot be adequately ensured if the imports are not subject to the same controls as domestic products. In addition, we believe that the importer who distributes a foreign product should share responsibility with the foreign manufacturer for safety. More often than not, it is a U.S. importer, rather than the foreign manufacturer, who actually distributes imported dietary supplements for sale in the United States. Thus, we believe that importers of dietary ingredients or dietary supplements should take steps to ensure that their shipments are obtained from manufacturers that follow these proposed CGMP requirements.

In addition, these proposed CGMPs would apply to manufacturers who export their dietary ingredient or dietary supplement, unless exported in compliance with section 801(e) of the act. Section 801(e)(1) of the act states that a food intended for export must not be deemed to be adulterated or misbranded under the act if it:

- Accords to the foreign purchaser's specifications;
- Is not in conflict with the laws of the country to which it is intended for export;
- Is labeled on the outside of the shipping package that it is intended for export; and
- Is not sold or offered for sale in domestic commerce.

Dietary ingredients and dietary supplements for export are subject to section 801(e)(1) of the act and would be subject to the notification and recordkeeping requirements of § 1.101 (21 CFR 1.101) and you would be required to comply with the export requirements of § 1.101.

We invite comment on whether we should require, in a final rule, that you make and keep records on the distribution of dietary ingredients and dietary supplements that you manufacture, package, or hold.

*G. Consumer Complaints—What Requirements Apply to Consumer Complaints? (Proposed Subpart G, § 111.95)*

Proposed § 111.95 would establish requirements for receiving and handling consumer complaints. Consumer complaints can be helpful in alerting you to possible manufacturing and safety problems associated with your dietary ingredients or dietary supplements.

As stated in § 111.3, consumer complaint refers to a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements of this part, including those that, if not met, may result in a possible risk of illness or injury. Proposed § 111.95(e) would require that you keep a written record of every consumer complaint that is related to good manufacturing practices. Thus, whether the complaint was sent by regular mail, electronic mail, or any other form of written communication, or whether received orally, you would be required to keep a written record of each consumer complaint. You should include all information that would allow your quality control unit to determine whether an investigation of the complaint is necessary.

Proposed § 111.95(a) would require that you have a qualified person review all consumer 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 specifications and other requirements that, if not met, may result in a possible risk of illness or injury. A ''qualified person'' would be a person who has the training and experience to determine whether a complaint represents a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements in this part, or represents a possible risk of illness or injury that is unrelated to such failure. The qualified person's review is important for distinguishing between those consumer complaints that your quality control unit must review and those consumer complaints that represent a consumer's dissatisfaction with a dietary ingredient or dietary supplement that is unrelated to a possible failure to meet specifications that would be required by this proposal, or any other requirement in this part. For example, some consumer complaints about quality may simply express a personal dislike of the taste, color, odor, or size of tablet, which would probably not require your quality control unit to review them. As stated earlier, consumer complaints related to an illness or injury related to a pharmacologically active substance of a particular dietary ingredient, such as aristolochic acid, would not be a consumer complaint within the meaning of that term in this proposal and thus would not be of the type that the quality control unit must review under this proposed rule.

Proposed § 111.95(b) would require that your quality control unit review all consumer complaints involving the possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any of the other requirements in this part, including those specifications and other requirements that, if not met, may result in a possible risk of illness or injury, to determine whether there is a need to investigate the consumer complaint. When there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event, such as a report of an illness or injury that may be due to a wrong ingredient or wrong label, then the manufacturer would be required to do an investigation that includes both batch records associated with the

dietary ingredient or dietary supplement involved in the consumer complaint. However, if the quality control unit determines that an investigation is unnecessary, it would be helpful to you if your quality control unit documents why an investigation was not necessary. This information would be useful to you because it could save time if you receive additional similar consumer complaints about a particular product.

Proposed § 111.95(c) would require that your quality control unit investigate a consumer complaint when there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event. For example, if a manufacturer uses too much of a dietary ingredient in a dietary supplement (*e.g.*, 400 to 4,699 µg of selenium instead of 200 µg of selenium), it is a manufacturing error that may result in an adverse event. Further, if a communication alleges consumer dizziness, vomiting, or lightheadedness after consuming several dietary supplements, it is a adverse event report that is worthy of quality control unit investigation.

Proposed § 111.95(d) would describe what the quality control unit's investigation must include. In brief, the quality control unit's investigation of a consumer complaint must include the batch records associated with the dietary ingredient or dietary supplement involved in the consumer complaint. The quality control unit must extend the investigation to other batches of dietary ingredients or dietary supplements that may have been associated with a failure to meet a specification or any other requirements of this part. When there is a possible product defect or failure, we recommend that the investigation include laboratory testing of the dietary ingredient or dietary supplement because you will need the test results to determine if specifications or requirements for the dietary ingredient or dietary supplement were not met. Complaints such as those that involve serious adverse events should include followup by a health care provider. For other types of complaints, neither laboratory nor medical investigation may be necessary because the product defect or failure may be identified by reviewing batch documents or the consumer complaint may not involve a serious adverse event.

Proposed § 111.95(e) would require that you make and keep a written record of every consumer complaint that is related to good manufacturing practices. 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. The consumer complaint written record must include, but is not limited to, the following:

- The name and description of the dietary ingredient or dietary supplement;
- The batch or lot number of the dietary supplement, if available;
- The complainant's name, if available;
- The nature of the complaint, including how the consumer used the product;
- The reply to the complainant, if any; and
- Findings of the investigation and followup action taken when an investigation is performed.

We suggest that you report the consumer complaint and the investigation results to us when there is a possibility of a relationship between the consumption of a dietary supplement and a serious adverse event. While the proposal would not require that you submit these reports, we strongly suggest that you do so because we may have additional expertise or data that may be helpful in investigating the complaint or determining whether the problem applies to more than one product. We suggest that you submit these reports within 15 days after you receive such information to the FDA MedWatch program by calling our ''MedWatch'' program (our database for reporting possible adverse events) at 1–800–FDA–1088 (1–800–332–1088) to request that a reporting form (one-page, return postage paid) and instructions on how to complete the form be mailed to you, downloading a form and instructions from the MedWatch Internet site at *http://www.fda.gov,* or using the interactive form available on the MedWatch Internet site at *http://www.fda.gov*.

Further, we suggest that you report a consumer complaint even if you are not the manufacturer of a dietary ingredient or dietary supplement and only package or distribute a dietary ingredient or dietary supplement if you receive a consumer complaint that may be related to the manufacture of the dietary ingredient or dietary supplement. Sometimes consumers submit complaints to the person who distributes a product or the person who is listed on the package label. If this happens, you should notify the manufacturer of the dietary ingredient or dietary supplement of the consumer complaint because the manufacturer may not be aware of possible problems associated with its products.

Proposed § 111.95(f) addresses documentation and recordkeeping. Consumer complaints can alert you (and us) to potential quality problems with a product that is related to good manufacturing practices, such as cases where the manufacturer used the wrong ingredient or put the wrong label on a product. A prudent manufacturer, therefore, must investigate any complaints regarding its products because the results of its investigations might lead to solutions or improvements that will make the product or manufacturing process better and benefit the manufacturer and consumers.

Proposed § 111.95(f)(1) would require the person who performs the requirement established in accordance with this section to document, at the time of performance, that he or she performed the requirement.

Finally, proposed § 111.95(f)(2) would require that you keep consumer complaint records established in accordance with proposed § 111.125. These records are necessary for handling consumer complaints in a manner that ensures that an unanticipated problem with a dietary ingredient or dietary supplement is reviewed and investigated. These records also are necessary to demonstrate compliance with the CGMP.

We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for receiving, reviewing, and investigating consumer complaints. 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.

*H. Records and Recordkeeping—What Requirements Apply to Recordkeeping? (Proposed Subpart H, § 111.125)*

Throughout this discussion of the proposed rule, some provisions have included a paragraph that would require

that you keep records established in accordance with proposed § 111.125. Proposed § 111.125 would establish general recordkeeping requirements and tell you how long you must keep certain records. As we have stated several times in this document, we determine CGMP compliance by conducting inspections. Records, therefore, enable you to show, and for us to determine, how you complied with the CGMP requirements.

Proposed § 111.125(a) would apply to all records covered by the proposed rule and would require that you keep those records for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with those records. Retention for 3 years beyond the date of manufacture would be appropriate for followup of consumer complaints received during the marketing period.

Proposed § 111.125(b) would deal with the form in which you keep records. The proposal would allow you to keep records required under this part as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records. If you use reduction techniques, such as microfilming, the proposal would require that you make suitable reader and photocopying equipment readily available to us. If you use electronic records, the proposal would require that you comply with part 11 (our requirements for electronic records).

Proposed § 111.125(c) would require that you make your records available for inspection and copying by us when requested. We sometimes need to copy records when our field inspectors need guidance or additional expertise from our headquarters staff; if we were unable to copy records, our inspections would become more complicated and longer in duration, particularly if the inspection involved a complex scientific or technical issue that normally would be handled at FDA headquarters.

## IV. Statement Concerning the Use of Plain Language

In response to the June 1, 1998, White House Presidential Memorandum on Plain Language, we drafted this proposed rule in plain language. Plain language is intended to help readers find requirements quickly and understand them easily. To do that, we have reorganized sections modeled after existing regulations and reworded the paragraphs using:

- Short sections, paragraphs, sentences, and words to speed up reading and enhance understanding;
- Sections as questions and answers to focus sections better; and
- Personal pronouns to reduce passive voice and draw readers into the text.

In some cases, we modeled a proposed provision after an existing regulation, but wrote the proposed rule using plain language techniques. We invite the public to comment on the plain language techniques used in this proposed rule. In developing your comments, please consider addressing the following points:

- Do you like the proposed rule's appearance?
- Do plain language techniques make the document easier to read and understand? and
- Do you have other suggestions to improve the format?

## V. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these requirements is given below with an estimate of the annual recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

*We invite comments on:* (1) Whether the proposed collection of information is necessary for the proper performance of our functions, including whether the information will have practical utility; (2) the accuracy of our estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including the use of automated collection techniques, when appropriate, and other forms of information technology.

*Title:* Current Good Manufacturing Practice in Recordkeeping and Reporting for Dietary Ingredients and Dietary Supplements.

*Description:* 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.'' Other relevant legal authority is discussed in section II of this document.

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. Under section 701(a) of the act, we may issue regulations necessary for the efficient enforcement of the act. If you did not keep records, for example, documenting practices performed during previous production runs, it would be difficult for us to determine whether, as stated under section 402(g)(1) of the act, the dietary supplement had been manufactured, packaged, and held under CGMPs. By requiring records, we will be able to ensure that you follow CGMPs and that your dietary supplements are not adulterated and misbranded during manufacturing, packaging, or holding operations.

The proposed rule would establish the minimum manufacturing practices necessary to ensure that dietary supplements are manufactured, packaged, or held in a manner that will not adulterate and misbrand the dietary ingredients or 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, and (7) records and recordkeeping.

We are proposing recordkeeping requirements that include records pertaining to: (1) Calibration of instruments and controls; (2) automatic, mechanical, or electronic equipment calibration, inspection, or checks; (3) production and process controls; (4) quality control; (5) receiving components, dietary supplements, packaging, and labels; (6) master manufacturing and batch production; (7) packaging and label operations; (8) returned dietary ingredients or dietary supplements; and (9) consumer complaints.

*Description of Respondents:* Dietary ingredient manufacturers, dietary supplement manufacturers, packagers and repackagers, distributors, warehousers, exporters, importers, large businesses, and small businesses.

We estimate the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

| 21 CFR Section | Number of recordkeepers | Annual frequency of recordkeeping | Total annual records | Hours per record | Total hours |
|---|---|---|---|---|---|
| 111.15(b)(3) | 231 | 12 | 2,772 | 0.1 | 277 |
| 111.15(d)(3) | 231 | 260 | 60,060 | 0.25 | 15,015 |
| 111.25(d) | 213 | 365 | 77,745 | 0.5 | 38,873 |
| 111.30(b)(2) and (b)(5) | 707 | 260 | 183,820 | 0.5 | 91,910 |
| 111.35(d) | 10 | 1 | 10 | 10 | 100 |
| 111.35(e) | 367 | 260 | 95,420 | 0.25 | 23,855 |
| 111.35(f) | 367 | 260 | 95,420 | 0.1 | 9,542 |
| 111.35(i)(1) | 367 | 10 | 3,670 | 0.25 | 918 |
| 111.35(j) | 367 | 260 | 95,420 | .25 | 23,855 |
| 111.35(m) | 367 | 365 | 133,955 | 0.1 | 13,396 |
| 111.37(b)(1), (b)(3) through (b)(5), (b)(7) through (b)(10), and (b)(12)(i) | 286 | 260 | 74,360 | 0.5 | 37,180 |
| 111.37(c) | 286 | 365 | 104,390 | 0.5 | 52,195 |
| 111.40(a)(3), (a)(4), (b)(2), and (b)(3) | 449 | 365 | 163,885 | 0.1 | 16,389 |
| 111.40(c)(1) | 218 | 365 | 79,570 | 0.5 | 39,785 |
| 111.45(a) [2] and (b) [2] | 200 | 1 | 200 | 30 | 6,000 |
| 111.50(a) through (c), (d)(1), and (e) | 68 | 260 | 17,680 | 1 | 17,680 |
| 111.50(g) | 68 | 260 | 17,680 | 0.5 | 8,840 |
| 111.60(b)(2) | 133 | 365 | 48,545 | 1 | 48,545 |
| 111.60(d) [2] | 133 | 1 | 133 | 3 | 399 |
| 111.65(c)(7), (c)(10), and (c)(11) | 133 | 365 | 48,545 | 0.1 | 4,855 |
| 111.70(b)(5) through (b)(6), (d), and (e) | 245 | 260 | 63,700 | 0.1 | 6,370 |
| 111.70(g) | 245 | 260 | 63,700 | 0.50 | 31,850 |
| 111.74(a) | 200 | 12 | 2,400 | 0.1 | 240 |
| 111.82(a) | 53 | 52 | 2,756 | 0.1 | 276 |
| 111.85(a) | 53 | 260 | 13,780 | 0.1 | 1,378 |
| 111.85(d) and (e) | 53 | 260 | 13,780 | 0.5 | 6,890 |
| 111.95(e) | 53 | 75 | 3,975 | 0.1 | 398 |
| 111.95(f)(1) | 93 | 75 | 6,975 | 0.5 | 3,488 |
| 111.125 | 220 | 4 | 880 | 0.1 | 88 |
| Total | | | | | 500,587 |

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] One time burden.

The burden estimates above are based on our institutional experience with CGMP requirements for drugs and on data provided by Research Triangle Institute (RTI) in the ''Survey of Manufacturing Practices in the Dietary Supplement Industry'' (Refs. E1 and E2). We tentatively conclude that there are no capital costs or operating costs associated with this proposed rule. However, we invite comments on information provided in table 1 of this document or on any anticipated costs.

The estimates for number of firms affected by each provision of the rule are based on the percentage of manufacturers, ingredient suppliers, repacker/relabelers, distributors, and warehousers that reported to RTI that they have not established or do not maintain records that would be required or recommended under the proposed rule. The RTI survey estimated that 1,566 firms would be covered by this rule including manufacturers, dietary ingredient suppliers, repacker/relabelers, distributors, and warehousers. The time estimates include the burden involved in documenting that certain requirements are performed and in recordkeeping. We used an estimated annual batch production of 260 batches per year to estimate the burden of requirements that are related to the number of batches produced annually, *e.g.*, proposed § 111.50, ''What requirements apply to establishing a batch production record?'' The estimate of 260 batches per year is near the midpoint of the number of annual batches reported by RTI survey firms.

Proposed § 111.125 prescribes the length of time for which CGMP records must be maintained. The burden chart reflects the estimated annual burden for record maintenance, for periodically reviewing records to determine if they may be discarded, and for any associated documentation for that activity for records that would be required under part 111. To avoid double-counting, we have not included a separate estimate of burden for those sections that would require maintaining records in accordance with proposed § 111.125, but have included a single burden estimate for all such records maintenance under proposed § 111.125. For example, proposed § 111.50(a) would require that the batch production records be prepared every time a batch is manufactured and § 111.50(i) would require that batch production records be kept in accordance with proposed § 111.125. The estimated burden for establishing the batch production records is counted in proposed § 111.50(a) and the estimated burden for keeping the batch production records as would be required in accordance with § 111.50(i) is counted in proposed § 111.125.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for its review. Interested persons are requested to send comments regarding information collection to the Office of Information and Regulatory Affairs, OMB (*see* **ADDRESSES**).

## VI. Environmental Impact Considerations

The agency has determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore,

neither an environmental assessment nor an environmental impact statement is required.

## VII. Analysis of Impacts

### *A. Introduction*

FDA has examined the economic implications of this proposed rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets anyone of a number of specified conditions, including: Having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. FDA has determined that this proposed rule, if it were to become a final rule, would be a significant regulatory action as defined by Executive Order 12866.

The Small Business Regulatory Enforcement Fairness Act of 1996 (Pub. L. 104–121) defines a major rule for the purpose of congressional review as being likely to cause one or more of the following: an annual effect on the economy of $100 million; a major increase in costs or prices; significant adverse effects on competition, employment, productivity, or innovation; or significant adverse effects on the ability of U. S.-based enterprises to compete with foreign-based enterprises in domestic or export markets. In accordance with the Small Business Regulatory Enforcement Fairness Act, OMB has determined that this proposed rule, when final, will be a major rule for the purpose of congressional review.

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. FDA finds that this proposed rule would have a significant economic impact on a substantial number of small entities.

We carry out the cost-benefit analyses required for significant rules in the Preliminary Regulatory Impact Analysis, in section VII.B of this document. We perform the Initial Regulatory Flexibility Analysis of the effects on the proposed rule on small businesses in section VII.C of this document.

### *B. Preliminary Regulatory Impact Analysis*

#### 1. The Need for the Proposed CGMP Regulations

The proposed CGMP regulations are needed because establishments that manufacture, package, and hold dietary ingredients and dietary supplements may not have sufficient market incentives to use controls to prevent the adulteration and misbranding of dietary ingredients or dietary supplements, including incentives to ensure their identity, purity, quality, strength, and composition (product quality). Manufacturing, packaging, and holding practices that ensure product quality can be costly, so establishments may not adopt them unless required to do so by regulation. Without the proposed regulations consumers of dietary supplements cannot be assured that all establishments are manufacturing dietary supplements in a way that ensures that these products are not adulterated or misbranded.

Manufacturing, packaging, and holding practices can compromise safety if they fail to prevent biological, chemical, and physical contamination, or if the wrong dietary ingredients are used that present an unreasonable risk of illness or injury. Strength (which is the amount of a specific dietary supplement or dietary ingredient in each tablet or capsule) that differs from label statements, missing or extra ingredients, and inconsistency across units of the product are other problems caused by poor manufacturing practices. Products may also be held in insanitary or environmentally inappropriate conditions, or may be physically damaged if stored improperly. Some poor manufacturing practices, such as the use of ingredients that are undeclared, of incorrect strength, or missing altogether result in a misbranded product. The proposed CGMP regulations would establish minimum requirements to ensure that manufacturing, packaging, and holding practices ensure the identity and quality of components, dietary ingredients, and dietary supplements.

Consumers today rely on manufacturer's assurances, existing regulations and statutes (for example, section 402(a)(3) and (a)(4) of the act), and recourse to the legal system to ensure that products are not defective. Brand names convey some information to consumers about a firm's manufacturing practices. Some private organizations, such as the National Nutritional Foods Association and the USP design minimum product standards or manufacturing requirements. The current act contains some provisions that prevent using putrid substances and insanitary manufacturing practices. In addition, either the threat of litigation or consumers seeking compensation for defective products and adverse health events may create incentives for establishments to adopt good manufacturing practices.

Actions by manufacturers, primarily voluntary quality controls, do not provide sufficiently protective industry-wide minimum requirements for manufacturing, packaging, and holding of dietary ingredients and dietary supplements. Without the proposed regulations, survey evidence shows that products in the dietary supplement market are sorted somewhere between two types:

- Higher-priced products with brand names or industry certification that follow several of the good manufacturing practices proposed here;
- Lower-priced products that contain no private certification or respected brand name and that follow few of the good manufacturing practices that are proposed here.

Without the proposed rule, the current practices do not provide all consumers with safe manufacturing practices or reliable product quality throughout the industry.

The market for dietary supplements is full of information; consumers of dietary supplements must sort through information and misinformation about the properties of these products from magazines, brochures, popular books, television, and a host of other sources. However, the information from these sources deals most often with the claims for the products themselves, not with the steps taken by establishments to protect against contamination or to ensure quality. Private quality control fails to provide industry-wide minimum good manufacturing practices for the following reasons:

- Establishments do not have incentives to disclose information about their own practices, because disclosure that some consumers may perceive to be harmful or undesirable would reduce the demand for their products. Establishments therefore have incentives to withhold information from consumers.
- Businesses normally do not advertise differences in manufacturing

practices. They seldom have access to competitors' proprietary information, and they may fear that advertising based on differences in practices would discredit the entire industry.

• Without public disclosure of product quality and adverse health events, the link between manufacturing practice and health hazard is difficult to establish. The link is probabilistic, requires data pooling across products and establishments (in order to establish cross sectional variation), and can be interpreted in a variety of ways.

• Because many consumers already mistakenly believe that the Federal Government guarantees safety, businesses have weak incentives to adopt good manufacturing practices, which are costly. In one recent survey of the nation's consumers, 34 percent report that they believe that the government regulates dietary supplements to ensure safety and that products do what they claim to do. (For details of the survey, *see* Ref. E3.) If people believe that good manufacturing practices are already followed, manufacturers may believe they gain little from voluntarily adopting them.

Information about manufacturing practices for dietary supplements is imperfect and costly to produce, so well-informed people should be willing to pay for improvements in the quality of information. An important benefit of the proposed regulations will be to reduce variation in manufacturing practices and ensure minimum quality for dietary supplement products. Reducing the variation in product quality by creating industry-wide minimum requirements reduces the information consumers now attempt to get through costly and uncertain sources in order to make purchasing decisions.

2. Regulatory Options

FDA considered several regulatory options for dealing with current manufacturing, packaging, and holding practices that may not ensure product quality. The options considered include: (a) No new regulatory action, (b) fewer requirements for vitamins and minerals, (c) more restrictive regulations than the proposed CGMP regulations, (d) HACCP without the other elements of CGMP regulations, (e) final product testing only, (f) regulations for high-risk products or hazards only, and (g) the proposed rule.

a. *No new regulatory action.* Under this option, consumers would probably rely on the following as protection against defective products:

• Possible enforcement action by FDA under, for example, section 402(a)(3) and (a)(4) of the act, regarding adulterated foods that consist of filthy, putrid, or decomposed substances or foods that have been prepared, packed, or held under insanitary conditions so that they may become contaminated or may be rendered injurious to health;

• Publicity from private consumer groups or health agencies on the risks from products not manufactured using CGMP regulations, manufacturers assurances, and the voluntary adoption of some or all provisions of the proposed regulations;

• Current or enhanced State and local enforcement activity to bring about a reduction of potential harm from contaminated or poor quality dietary supplements; or

• Litigation or the threat of litigation by consumers who allege harm from consumption of the dietary supplement.

We believe that there are compelling reasons not to rely on these alternatives alone.

If public and private health agencies, consumer groups, competitors, trade organizations or other third parties publicized the risks from products not manufactured using private good manufacturing practices, then consumers would decide for themselves on the risks of contaminated or poor quality products. The weakness of this alternative is that third-party organizations cannot easily discover many of the problems caused by poor manufacturing practices because manufacturers are reluctant to voluntarily share information to third parties about their manufacturing practices.

Actions by manufacturers, such as by voluntarily introducing good manufacturing practices, occur when the expected private economic benefits of the actions exceed the private costs. Voluntary adoption of good manufacturing practices will occur when it is profitable to do so. Many establishments appear to be adopting some publicly available good manufacturing practice models in order to meet the demand for safer and more uniform products. NNFA is implementing a good manufacturing practice certification program. The USP sets standards for strength, purity, disintegration, and dissolution for individual and combination vitamins and minerals. Also, Consumerlab.com is introducing a certification label, CL, to show when ingredients meet their minimum requirements. However, 36 percent of recently surveyed dietary supplement establishments do not follow any good manufacturing practice models for their products (Ref. E2). The breakdown of survey results shows that 48 percent of very small firms, 27 percent of small firms and 11 percent of large firms do not follow a good manufacturing practice model. The survey results also show that 32 percent of vitamins and mineral establishments, 39 percent of amino acid/protein/animal extract establishments, 41 percent of herbal and botanical establishments, and 59 percent of establishments not already classified, do not follow a good manufacturing practice model.

Without industry-wide uniform requirements, some establishments may follow different practices but convey the message that they follow good manufacturing practices. In short, people who want to discriminate between establishments that use good practices and those that do not would not have sufficient information to do so. Another reason for our skepticism about universal voluntary adoption of good manufacturing practices is that good practices appear to be taken for granted by many consumers. Indeed, some consumers already believe that the Federal Government regulates the manufacturing practices of the industry, so firms lack an incentive to provide additional assurance (Ref. E3).

Current or enhanced State and local regulations could bring about a reduction of potential harm from contaminated supplements. This alternative has the advantage that State and local governments can exercise more discretion when responding to local manufacturing conditions or consumer health practices than the Federal Government. Because most of the industry engages in interstate commerce, however, Federal regulations are appropriate. Also, Federal regulations would apply uniformly across the country, whereas State and local regulations might impose different standards on establishments that supply supplements across State and local boundaries.

Litigation or the threat of litigation may help to bring about the goals of the proposed rule. The potential of costly litigation from the harm caused by deficient manufacturing practices creates an incentive for manufacturers to reduce the risks from defective products. However, we do not believe that litigation or the threat of litigation has created the incentives for all manufacturers to implement the manufacturing practices that we believe are necessary to avoid adulterated or misbranded products. As discussed earlier, not all surveyed dietary supplement manufacturers reported that they followed good manufacturing practices. Furthermore, in some cases it is difficult and costly to demonstrate to the courts that the harm to plaintiffs was

actually the result of poor manufacturing practices, making recourse to the courts sometimes impractical.

In the absence of the proposed CGMP regulations, the burden of monitoring manufacturing practices would fall more heavily on consumers, despite the difficulties consumers face in monitoring manufacturers. Moreover, the proposed CGMP regulations are preventative and should ensure that problems are identified and dealt with during manufacturing, packaging, and holding, rather than after someone has consumed an unsafe product and experienced an adverse effect.

b. *Fewer requirements for vitamins and minerals.* FDA could require more controls from establishments that manufacture, package, or hold plant or animal derived dietary ingredients such as amino acids, proteins, herbals, botanicals and other products not classified as vitamin and mineral manufacturers, packagers, or holders. The plant or animal derived dietary ingredients are probably characterized by greater variation in product quality than synthetically derived dietary ingredients. Under this option, the segment of the industry that manufacture, package, or hold products that are the most likely to have difficulty manufacturing or maintaining uniform product quality dietary ingredients would be required to follow the proposed testing and other production and process control requirements. Manufacturers of vitamins and minerals would be required to follow the sanitation, holding, and consumer complaint provisions only, they would not have to adopt manufacturing controls to ensure that products did not contain too much or too little of a vitamin or mineral.

Plant or animal ingredients are likely to experience greater natural variation in product quality than synthetic compounds, so they may require the higher minimum standard of regulation contained in the proposed regulation. The advantage of this option is that fewer establishments will be affected as much; approximately 723 establishments classified as manufacturers, packagers or holders of products other than vitamins and minerals, rather than the 1,566 establishments estimated to be covered by the proposed regulation (*see* table 2 of this document). The compliance costs would therefore be lower. The disadvantage is that vitamin and mineral manufacturers also potentially manufacture products of variable quality, so the expected benefits from more consistent product quality would be reduced. Moreover, if dietary supplements contain too little of a vitamin or mineral consumers may not receive the intended health benefits, and if the dietary supplements contain too much of a vitamin or mineral they may experience illness or injury.

We estimate that the benefits of this option would be approximately proportional to the ratio of recalled products that were classified as vitamins and minerals to all recalled dietary supplements products. Approximately 50 percent of the recalled products were vitamins and minerals so we estimate that this option would generate no more than $109 million in benefits. We assumed that the costs of this option would be proportional to the fraction of establishments that would be required to follow all of the proposed provisions and those that follow the reduced requirements with the total costs estimated for this proposal as shown in table 17 of this document. The estimated mean cost of the proposed regulation is $86 million (see table 19 of this document). The fraction of establishments required to follow all the provisions is .46 (= 723/1566). The fraction of establishments that would have reduced testing is .54 (= 843/1566). Testing is approximately 36 percent of the total costs. We estimate the total costs from this option to be $69 million ($86 million $\times$ .46 + $86 million $\times$ .54 $\times$ (1 $-$ .36)).

c. *More restrictive CGMP regulations than the proposed regulations.* One option is to propose (or finalize) more restrictive rules than the proposed CGMP regulations. Under this option, CGMP regulations could provide consumers with additional safeguards. Several of the largest manufacturers of dietary supplements now voluntarily comply with some of these additional safeguards (Ref. E2). The most significant additional provisions that would be required under this option are product quality testing for each incoming shipment lot of components and dietary ingredients, inprocess testing for contaminates at critical control points and mandatory written procedures for all of the various provisions of the proposed regulation.

The advantage of this option is that the additional requirements provide safeguards that the essential safety and quality provisions are being followed. The disadvantage of this option is that it is more costly than the proposed rule, and we are not aware of any information that would show any additional verifiable health benefits.

d. *HACCP without the other elements of CGMP regulations.* The agency could propose a requirement that manufacturers implement a HACCP (or HACCP like) system for the manufacturing of dietary supplements without the other elements of the proposed CGMP regulations. A critical control point is where production controls can be applied to reduce or eliminate hazards (including biological, chemical, or physical contamination) that may make dietary supplements unsafe.

The advantage of an industry-wide HACCP program is that HACCP does not require manufacturers to follow detailed uniform requirements in order to achieve desirable outcomes. Manufacturers themselves determine for their specific products and processes how they will best eliminate, reduce, or control hazards in the manufacturing of dietary supplements.

We have not designed a hypothetical HACCP system for the dietary supplement industry. For the purpose of generating estimates of costs and benefits, we assumed that a HACCP regulation for a dietary supplement manufacturer would be likely to encompass sanitation prerequisites that are met, writing a HACCP plan, and monitoring critical control points. The benefits and costs of the HACCP plan would be generated by controls for a narrower set of hazards in the manufacturing, packaging, and holding processes than those covered by this proposal, and would not include the other benefits and costs generated by the proposed rule especially the reduced consumer search costs, because uniform product quality would not necessarily be assured. The advantage of HACCP as an option to prevent product contamination is that it does not specify detailed manufacturing requirements. The disadvantage is that in the absence of uniform controls there would not be uniform minimum product quality across the industry and consumers would not derive the same benefits from lower search costs.

e. *Require final product testing only.* FDA could propose that manufacturers test their finished products for identity, purity, quality, strength, and composition but not include any of the other mandatory provisions of the proposed regulation. The advantage of this option is that it would be the least costly option of those considered. Many firms already test some of their finished products, reducing the impact of this option. Approximately 69 percent of manufacturing plants conduct finished product testing and almost 65 percent of all finished batches in the industry are already tested using physical, chemical, microbiological, visual or organoleptic

testing techniques (Ref. E2). The problem with this option is that finished product testing alone cannot ensure product quality for some types of products. Not every finished product currently has a test that confirms identity, purity, quality, strength, or composition, especially for multiingredient products. Tests may not have been developed, or they may not be completely reliable, or they may not be capable of evaluating every type of product defect. Also, potentially lower cost alternatives to finished product testing—such as incoming component lot testing, inprocess testing, or both—might be available and desirable to firms as a means to protect the public. Moreover, finished product testing alone is not sufficient to prevent products with microbiological or chemical contamination from being discovered because it is possible that false negatives might occur, as when there is ''hotspot'' contamination within a batch. Preventative controls must be imposed to achieve that goal. Finally, finished product testing alone also will not facilitate trace backs when defective products are discovered in the marketplace, nor will it facilitate responsible investigations of consumer complaints. The estimated cost of this option is lower than that of the other options, but it does not generate the full range of benefits provided by the proposed rule.

f. *Regulate only high-risk products.* FDA could propose CGMP regulations that would cover only high-risk products. The advantage of this option is that it would impose lower costs than the proposed rule, but (if all risky products could be identified and regulated) generate the same level of benefits. Only those establishments that manufacture high-risk products or have high-risk hazards would incur the costs of adopting CGMP regulations. High-risk might be defined as those products most likely to be contaminated, or suffer other product defects. There are two problems with this option. Adverse event reporting is not mandatory, so significant underreporting is expected. Also, it is possible that the confirmed illnesses and other problems linked to particular dietary supplements may be those most easily traced, rather than those with the highest risk. High levels of identified problems may not be closely correlated with high levels of risk. In other words, problems associated with the known defective products may or may not be correlated with the highest risk. Without more data and risk assessments, it would be difficult to distinguish what risks may be associated with particular dietary supplements. We therefore have no basis upon which to begin a full evaluation of what the high-risk products are or may be.

3. Coverage of the Proposed Rule

The proposed rule would cover establishments that manufacture, package, hold dietary ingredients or dietary supplements. Tables 2, 3, and 4 of this document list the estimated number of covered manufacturers, packagers, dietary ingredient suppliers, holders, and other establishments. Table 2 of this document shows the number of covered establishments by product type and size. A small business, based on the Small Business Administration definition, is any firm with 500 or fewer employees. For purposes of analysis, we defined very small establishments as having fewer than 20 employees. Table 3 of this document shows the number of establishments categorized as manufacturers, ingredient suppliers, repackers or relabelers, holders whose primary business is dietary ingredients or dietary supplements, and other (although not including other holders and distributors). Table 4 of this document shows our estimate of the number of general warehouses and wholesalers that hold dietary supplements.

TABLE 2.—COVERED ESTABLISHMENTS BY PRODUCT TYPE AND SIZE FROM DIETARY SUPPLEMENT ENHANCED ESTABLISHMENT DATABASE (DS–EED)

| Product type | Very small | % | Small | % | Large | % | Unknown | % | Total |
|---|---|---|---|---|---|---|---|---|---|
| Vitamins and Minerals | 252 | 29.8 | 223 | 26.5 | 78 | 9.2 | 290 | 34.5 | 843 |
| Amino Acids, Proteins | 21 | 31.0 | 16 | 23.0 | 6 | 6.9 | 27 | 39.1 | 69 |
| Herbals and botanicals | 148 | 42.6 | 46 | 13.2 | 5 | 1.1 | 150 | 43.1 | 348 |
| Supplements not already classified | 93 | 30.4 | 66 | 21.6 | 20 | 6.5 | 127 | 41.6 | 306 |
| Total | 514 | 32.8 | 351 | 22.4 | 106 | 6.8 | 594 | 38.0 | 1,566 |

TABLE 3.—COVERED ESTABLISHMENTS BY TYPE OF OPERATION FROM DS–EED

| Establishment type | Number of establishments | Percent of establishments |
|---|---|---|
| Manufacturer | 1,228 | 78.4 |
| Dietary ingredient supplier | 106 | 6.7 |
| Repacker; relabeler | 26 | 1.7 |
| Holder | 114 | 7.3 |
| Establishments not already classified | 92 | 5.9 |
| Total | 1,566 | 100.0 |

TABLE 4.—COVERED ESTABLISHMENTS THAT HOLD DIETARY SUPPLEMENTS

| Type of holders | Source and SIC code | Number of establishments |
|---|---|---|
| Grocery Wholesalers or Drug Wholesalers | Dunn and Bradstreet: 5122, 5141 | 25,527 |
| Food or Drug Warehouse | Dunn and Bradstreet: N/A | 738 |
| Miscellaneous Food or Drug Warehouse | Dunn and Bradstreet: 4225, 4226, 5912, 5499, 5411, 5122, 5141, 5149, 5399, 5311, and 5331. | 238 |

TABLE 4.—COVERED ESTABLISHMENTS THAT HOLD DIETARY SUPPLEMENTS—Continued

| Type of holders | Source and SIC code | Number of establishments |
|---|---|---|
| Dietary Supplement | DS–EED | 114 |
| Total | | 26,617 |

We consulted several sources to estimate the number of establishments reported in tables 2, 3, and 4 of this document. The number shown in tables 2 and 3 of this document, 1,566, is the estimated number of establishments in the DS–EED that manufacture, repackage, supply dietary ingredients, or hold dietary supplement products in the United States. RTI developed the DS–EED using FDA's Official Establishment Inventory (OEI) and supplemented that source with information from trade organizations, trade shows, and electronic databases (Refs. E1 and E2).

The number of establishments in the DS–EED that hold dietary supplements is not the total number of holders covered by the proposed regulation. The holding establishments in the DS–EED identified holding dietary supplements as their primary business. To estimate the total number of establishments that could hold dietary ingredients or dietary supplements but do not consider dietary supplements as their primary business, we performed three searches of firms that are listed with Dun and Bradstreet's Dialog database. We first looked for a count of firms that had standard industrial classification (SIC) codes for wholesalers of groceries or drugs. Next we looked for a count of firms that met the description of warehouses of groceries or drugs (no SIC codes were used). Finally, we looked for a count of any firms that had both warehouse SIC codes and miscellaneous drug stores, food stores, sundries, and general merchandise (SIC 4225, 4226, 5912, 5499, 5411, 5122, 5141, 5149, 5399, 5311, and 5331). The results are shown in table 4 of this document. We concluded that the total number of establishments in this category that could hold dietary ingredients or dietary supplements and would be covered by the regulation was approximately the sum of the numbers counted in the three searches, or 26,617.

The number of establishments that hold dietary ingredients or dietary supplements includes retailers that sell dietary supplements to consumers, and transporters of dietary ingredients and dietary supplements. We made no effort to determine the number of such holders, because the proposed requirements do not apply to retailers and transporters. We believe that retailers and transporters may voluntarily adopt provisions related to the holding of these products and thus there may be changes in the marketplace with accompanying costs and benefits. However, we expect that the only retailers and transporters that will voluntarily adopt the proposed requirements are those that expect the private benefits of adoption will exceed the private costs.

4. Baseline Practices

a. *Consumer baseline practices.* Baseline consumer and manufacturer practices, governed by current market forces and existing government regulations, give rise to the current risks associated with the manufacturing of dietary supplements. When determining baseline manufacturing practices, it is necessary to estimate both the practices that are used now, as well as the likely changes in manufacturing practices that will occur even in the absence of new regulations. The risks to consumers from these products can be associated with a combination of consumption habits, the contamination of the products, or both. Contamination may be caused by current manufacturing practices. Consumption is influenced by the price and quality of dietary supplements, set by the interaction of market participants. Finally, changes in practices of either consumers or manufacturers caused by new regulatory requirements will give rise to changes in risks, as estimated by changes in costs and benefits.

The consumption of dietary supplements has grown in recent years. Consumers report that they are using a wider range of product types, and that they are using dietary supplements for more reasons than they were in the past.

Table 5 of this document illustrates the rapid sales growth of the dietary supplement industry from 1994 to 2000. Panel A of table 5 of this document shows annual sales of three general categories of dietary supplements, a measure of the market size of the supplement industry. Annual increases in sales of herbals and botanicals were the greatest, averaging 18 percent per year, while annual increases in sales of supplements that were neither vitamins and minerals nor herbals and botanicals increased less, averaging 11 percent per year. The lowest annual sales increases were for vitamins and minerals, averaging 8 percent per year. For all dietary supplements combined, sales increased an average of 12 percent a year since 1994 (not shown on the table).

While the sales growth shown in table 5 of this document, Panel A, is impressive, only part of this apparent growth represents increased use. Population growth and rising prices also contributed to the apparent growth. The real (growth inflation-adjusted) increase in dietary supplement prices is estimated by subtracting the inflation rate from the rate of price increases of dietary supplements (Ref. E4). As shown in table 5 of this document, Panel B, between 1995 and 1997 the real price of vitamins and minerals and supplements other than vitamins and minerals all increased. Rising real price indicates that demand is growing rapidly.

Table 5 of this document, Panel C, shows estimated annual increases in per capita consumption of dietary supplements.[1] As shown in table 5 of this document, Panel C, the estimated per capita consumption of the different categories of dietary supplements has increased since 1994.

For the consumption estimates in table 5 of this document, we averaged dietary supplement use over the entire U.S. population, 275 million. In table 6 of this document, we included estimated average supplement use for the population of supplement users, 160 million (Ref. E13). The three panels in table 6 of this document show the annual consumption per supplement user and the annual change in consumption per supplement user for

[1] An index measuring per capita consumption of dietary supplements can be derived using the following equation: $PCC_t = [1{,}000 \times Sales_t]/[POP \times P_t]$, where, t = year index; $PCC_t$ = per capita consumption (# of unit sales); Sales = millions of dollars of sales; $POP_t$ = thousands of U.S. residents; $P_t$ = average price of supplement. In the formula, we measure consumption as the number of dietary supplement units (bottles, packages, etc.) sold per U.S. resident for a given year.

vitamins and minerals, herbals and botanicals, and supplements other than vitamins and minerals and herbals and botanicals. Table 6 of this document also shows that during this period the proportion of consumers using supplements increased faster than the average consumption for the total population. The surprising implication of this result is that consumption per user has apparently declined since 1994.

One limitation of the estimates in table 6 of this document is that prevalence of supplement use is based on the proportion of U.S. adults consuming supplements, while the per capita consumption figures are based on the entire U.S. population. Nonetheless, we do not have any reason to believe that the estimated trend in consumption per user is biased. This trend, expressed as the percentage change in consumption per user, is negative for all segments of the dietary supplement industry since 1994. The large and rising number of consumers accounts for the growing size of the dietary supplement industry.

TABLE 5.—GROWTH IN MARKET SIZE AND PER CAPITA CONSUMPTION OF DIETARY SUPPLEMENTS, 1994–2000

| | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 |
|---|---|---|---|---|---|---|---|
| **Panel A—Nominal Market (Millions of Current Dollars)** | | | | | | | |
| Vitamins | 3,960 | 4,220 | 4,780 | 5,190 | 5,550 | 5,940 | 6,360 |
| Growth rate (percent) | ..... | 6.57 | 13.27 | 8.58 | 6.94 | 7.03 | 7.07 |
| Minerals | 700 | 800 | 900 | 1,070 | 1,160 | 1,250 | 1,350 |
| Growth rate (percent) | ..... | 14.0 | 13.0 | 19.0 | 8.0 | 8.0 | 8.0 |
| Herbals and Botanicals | 2,070 | 2,530 | 2,990 | 3,530 | 4,170 | 4,840 | 5,520 |
| Growth rate (percent) | ..... | 22.22 | 18.18 | 18.06 | 18.13 | 16.07 | 14.05 |
| Supplements other than vitamins/minerals and botanicals | 2,070 | 2,290 | 2,620 | 2,890 | 3,180 | 3,490 | 3,840 |
| Growth rate (percent) | ..... | 10.63 | 14.41 | 10.31 | 10.03 | 9.75 | 10.03 |
| Total | 8,080 | 9,840 | 11,290 | 12,680 | 14,060 | 15,520 | 17,070 |
| Growth rate (percent) | ..... | 12.0 | 15.0 | 12.0 | 11.0 | 10.0 | 10.0 |
| **Panel B—Prices** | | | | | | | |
| Consumer price index-units (percent) | 148.5 | 152.5 | 157.0 | 160.5 | 163.2 | 166.7 | ..... |
| Inflation rate (percent) | 2.56 | 2.76 | 2.957 | 2.23 | 1.68 | 2.14 | 2.39 |
| Vitamins and minerals | ..... | ..... | ..... | ..... | ..... | ..... | ..... |
| Average nominal price (IRI) | $6.20 | $6.50 | $6.87 | $7.34 | $7.54 | $7.78 | $8.05 |
| Nominal price increase (percent) | 2.69 | 4.84 | 5.69 | 6.84 | 2.72 | 3.18 | 3.43 |
| Real price increase (percent) | 5.25 | 2.08 | 2.74 | 4.61 | 1.04 | 1.04 | 1.04 |
| Supplements other than vitamins and minerals: | | | | | | | |
| Average nominal price | $6.20 | $6.50 | $6.87 | $7.34 | $7.70 | $8.11 | $8.56 |
| Nominal price increase (percent) | 5.80 | 4.84 | 5.69 | 6.84 | 4.85 | 5.31 | 5.56 |
| Real price increase (percent) | 3.24 | 2.08 | 2.74 | 4.61 | 3.17 | 3.17 | 3.17 |
| **Panel C—Per Capita Consumption (Number of Units Sold Per U.S. Resident)** | | | | | | | |
| Vitamin/mineral sales | 2.45 | 2.47 | 2.62 | 2.64 | 2.72 | 2.80 | 2.87 |
| Growth (percent) | ..... | 0.69 | 6.19 | 0.66 | 3.12 | 2.74 | 2.55 |
| Herbals sales | 1.28 | 1.48 | 1.64 | 1.80 | 2.00 | 2.19 | 2.34 |
| Growth (percent) | ..... | 15.48 | 10.79 | 9.45 | 11.60 | 9.17 | 7.03 |
| Supplements other than vitamins and minerals and herbals sales | 1.28 | 1.34 | 1.44 | 1.47 | 1.53 | 1.58 | 1.63 |
| Growth (percent) | ..... | 4.53 | 7.26 | 2.26 | 3.95 | 3.23 | 3.25 |

TABLE 6.—COMPARISON OF CONSUMPTION PER PERSON WITH CONSUMPTION PER USER: EVIDENCE THAT THE DIETARY SUPPLEMENT MARKET IS BECOMING BROADER NOT DEEPER

| Average Growth | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 1994–2000 |
|---|---|---|---|---|---|---|---|
| **A. Vitamins and Minerals** | | | | | | | |
| Per capita consumption (units per U.S. resident) | 2.45 | 2.47 | 2.62 | 2.64 | 2.72 | 2.80 | ..... |
| % Growth | ..... | 0.69 | 6.19 | 0.66 | 3.12 | 2.74% | 2.68% |
| Consumption prevalence (percent) | ..... | 47.70 | 54.0 | 61.0 | 70.0 | 79.0 | ..... |
| Reference | ..... | Ref. E6 | Ref. E6 | Ref. E6 | Ref. E6 | Ref. E7 | ..... |
| % Growth | ..... | ..... | 13.44 | 13.44 | 13.44 | 13.44 | 13.44 |
| Consumption per user (units) | ..... | 5.18 | 4.85 | 4.30 | 3.91 | 3.54 | ..... |
| % Growth | ..... | ..... | −6.39 | −11.27 | −9.10 | −9.43 | −9.05 |
| | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 1994–1999 |
| **B. Herbals and Botanicals** | | | | | | | |
| Per capita consumption (units per U.S. resident) | 1.28 | 1.48 | 1.64 | 1.80 | 2.00 | 2.19 | ..... |

TABLE 6.—COMPARISON OF CONSUMPTION PER PERSON WITH CONSUMPTION PER USER: EVIDENCE THAT THE DIETARY SUPPLEMENT MARKET IS BECOMING BROADER NOT DEEPER—Continued

| Average Growth | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 1994–2000 |
|---|---|---|---|---|---|---|---|
| % Growth | ..... | 15.48 | 10.79 | 9.45 | 11.60 | 9.17 | 11.30 |
| Consumption prevalence (percent) | 8.20 | 12.10 | 12.10 | 12.10 | 28 | 49 | ..... |
| Reference | Ref. E8 | Ref. E8 | Ref. E8 | Ref. E9 | Ref. E10 | Ref. E7 | ..... |
| % Growth | ..... | 47.56 | 0.00 | 0.00 | 131.40 | 75.00 | 50.79 |
| Consumption per user (units) | 15.64 | 12.24 | 13.56 | 14.84 | 7.16 | 4.47 | ..... |
| % Growth | ..... | −21.74 | 10.79 | 9.45 | −51.77 | −37.62 | −18.18% |
| **C. Supplements Other than Vitamins and Minerals and Herbals and Botanicals** | | | | | | | |
| Per capita consumption (units per U.S. resident) | 1.28 | 1.34 | 1.44 | 1.47 | 1.53 | 1.58 | ..... |
| % Growth | ..... | 4.53 | 7.26 | 2.26 | 3.95 | 3.23 | 4.24 |
| Consumption prevalence (percent) | 5.1 | 8.8 | 11.2 | 14.2 | 18.1 | 23.0 | ..... |
| Reference | Ref. E8 | Ref. E8 | Ref. E8 | Ref. E8 | Ref. E8 | Ref. E7 | ..... |
| % Growth | ..... | 72.55 | 27.15 | 27.15 | 27.15 | 27.14 | 36.23 |
| Consumption per user (units) | 25.15 | 15.24 | 12.85 | 10.34 | 8.45 | 6.86 | ..... |
| % Growth | ..... | −39.42 | −15.64 | −19.58 | −18.25 | −18.81 | −22.34 |

b. *Manufacturer's baseline practices.* FDA contracted with RTI to conduct a survey of the dietary supplement industry to learn about both baseline (existing) manufacturing practices and the existing standards used for manufacturing dietary ingredients and dietary supplements (Ref. E2). A sample of 966 dietary supplement establishments from the DS–EED database was selected from an estimated eligible population of 1,566 firms in the industry. The sample was stratified by manufacturer's product type and the size of firm in the industry. Stratification helps ensure that estimates of the subpopulations are more precise. Establishments that were stratified by manufacturer's product type were classified as primarily: (1) Vitamins and minerals; (2) amino acids, proteins, or animal extracts; (3) herbals and botanicals; or (4) all other product types not already classified. The product type strata were further stratified by four size categories: (1) Very small, (2) small, (3) large, and (4) unknown. This categorization generated 16 sampling strata.

The contractor, RTI, sent each of the 966 firms in the sample a lead letter on FDA letterhead and a one-page brochure to explain the purpose of the survey, the value of the establishment's participation, and the agency's confidentiality procedures. Following the mailing, RTI placed telephone calls to each establishment to screen for eligibility and to recruit eligible establishments for the mail survey. To be eligible for the survey, establishments had to currently manufacture, repackage, supply dietary ingredients, hold, import or export dietary supplements for human consumption. Almost 50 percent of the establishments sampled were not eligible for the survey because they were no longer in operation at the listed address or did not handle any dietary supplements or ingredients for human consumption.

To achieve the highest possible response rate, RTI operated a toll-free help line and attempted to contact each establishment up to eight times before assigning a disposition of nonresponse. RTI also attempted up to two refusals conversions, which are attempts to persuade firms that declined to answer the survey to respond. The survey was conducted over a 10-week period, November 29, 1999, to February 4, 2000. There were a total of 238 completed surveys, resulting in a final disposition of: (1) An overall eligibility rate of close to 50 percent, and (2) a response rate of 50 percent.

Determining baseline practices is necessary in order to determine the new activities that are likely to take place as a result of implementation of this proposed rule. Each of the new activities potentially brought about by the proposed rule has both a marginal (or incremental) cost and a marginal (or incremental) benefit. These incremental costs and benefits of likely new activities form the basis of our economic analysis of the proposed rule.

The survey asked establishments a series of questions about existing practices; we used the responses to estimate how many establishments in the industry already operated in accordance with the requirements of the proposed regulation. One key assumption in this analysis is that no firms are expected to stop CGMPs and no firms are expected to start good manufacturing practices in the absence of this rule. The universe for the survey includes the establishments discussed in section VII.B.3 of this document. If firms start good manufacturing practices in the absence of this rule, both the costs and benefits of the rule would be less than we estimate. If firms were to stop in the absence of the rule, both the costs and benefits would be more than we estimate. We lack information about the trend in the industry, so we assumed that the survey reflects both the current and future practices in the industry. We request comment or information about the industry trend in adopting good manufacturing practices.

i. *Stratification.* The survey was stratified by product type and establishment size. Stratification ensures that samples are representative of the industry population.[2] The subdivisions of the population of interest here were establishment size (by the number of employees) and product type, because these characteristics are likely to influence whether an establishment already has adopted the practices that would be required by the regulation. The DS–EED includes nine product types: (1) Vitamins and minerals; (2) herbals and botanicals; (3) herbal and botanical extracts; (4) amino acids; (5) proteins; (6) animal extracts; (7) tea like products; (8) concentrates, metabolites, or constituents; and (9) supplements not already classified (all other supplements). Establishments may produce more than one product type; establishments with multiple product types were, however, only classified in one category. For stratification and reporting purposes, we defined the

[2] Stratification is a subdivision of the population of establishments in the dietary supplement industry by a unique characteristic such as product type or number of employees.

following four mutually exclusive categories of dietary supplements:

1. Vitamins and minerals (includes establishments that may also manufacture, package, or hold herbals and botanicals, amino acids, proteins, or animal extracts but predominately manufacture vitamins and minerals);

2. Amino acids, proteins, and animal extracts (includes establishments that also manufacture, package or hold herbals and botanicals, including extracts; excludes establishments already classified as vitamins and minerals);

3. Herbals and botanicals, including extracts (excludes establishments already classified as ''vitamins and minerals'' or ''amino acids, proteins, or animal extracts''); and

4. Supplements not already classified (all other product types).

We further stratified each of the four product categories into four size categories, very small, small, large, and unknown—resulting in 16 sampling strata. We classified each establishment into one mutually exclusive industry category (manufacturer, dietary ingredient supplier, repacker/relabeler, holder, or establishment not already classified). Establishments that manufacture supplements and also supply, repack, or hold dietary supplements or ingredients were classified as manufacturers.

ii. Size stratification. The Small Business Administration classifies companies as ''small'' based on the size of the entire company, including both parent and subsidiaries. If firms that manufacture dietary supplements have 500 or fewer employees, they are classified as small. Because the DS–EED data on size are only for specific establishments and not parent firms, we had to obtain parent company information on employment or revenue to correctly classify each establishment as part of a small or large company. To obtain parent company data for establishments in the survey universe, we sent *Info*USA [3] the DS–EED data records (N = 2,004) and requested the name, address, primary SIC, employment size (in ranges), and revenue (in ranges) of parent company firms with establishments in the survey universe. *Info*USA matched 1,219 of the 2,004 records in the DS–EED to their U.S. database of 10.3 million businesses. Of the 1,219 matched records, 31 records were found to be duplicates of another record and were removed, leaving 1,188 matched records and 1,566 total records in the sampling frame. The nonmatched records did not match because: (1) They were recently established businesses, (2) they were out of business, or (3) they had recently changed their names or addresses. Because data on revenue or employment size were not available for the nonmatched records, we created an ''unknown'' stratum for these establishments. The survey of practices collected information on employment that allowed us to classify some of these establishments by size for the analysis.

Of the 1,188 matched records, 180 were linked to parents. The parent company data for these 180 establishments were merged with the survey universe. The remaining 1,008 records did not link to an ultimate parent company. For these records, the establishment and parent company were the same entity, so we used establishment level data to classify size. We classified each of the establishments in the survey universe as part of very small, small, or large businesses based on the employment size or annual revenues of each establishment's parent company. If an establishment or its parent company had 500 or fewer employees or sales less than $20 million (if data on employment were not available), then the establishment was classified as small. An establishment was classified as very small if the number of employees was less than 20.

iii. *Survey response.* Table 7 of this document presents the number of establishments surveyed, stratified by the four product types and by size. Although the sample allocation was designed to yield 400 completed surveys, we received only 238 completed mail surveys. The number of respondents was fewer than expected because the number of establishments that were ineligible was greater than we expected and because some establishments did not respond to the survey after agreeing to participate. Ineligible establishments are those that no longer produce dietary supplements because they have gone out of business or changed product lines, or they have moved and could not be located. Despite receiving fewer responses than planned, the confidence level for the final results allowed us to make meaningful inferences regarding the industry. For example, 65 percent of the establishments surveyed responded that they followed published good manufacturing practice models; the 95 percent confidence interval was 56 to 72 percent. By size category, 52 percent of very small, 73 percent of small, and 89 percent of large establishments responded that they followed published good manufacturing practice models (Ref. E2). Although we do not suggest that these percentages are precise, they do tell a plausible story of the current use of good manufacturing practice models in the supplement industry: The use of good manufacturing practice models appears to be widespread but far from universal, with use more likely the larger the establishment.

TABLE 7.—NUMBER OF COMPLETED SURVEYS BY SAMPLING STRATA

| Product type | Size | | | | |
|---|---|---|---|---|---|
| | Very small | Small | Large | Unknown | Total |
| Vitamins and minerals | 19 | 39 | 13 | 1 | 72 |
| Amino acids, proteins | 8 | 7 | 0 | 5 | 20 |
| Herbals and botanicals, including extracts | 58 | 25 | 0 | 30 | 113 |
| Supplements not already classified | 14 | 13 | 2 | 4 | 33 |
| Total | 99 | 84 | 15 | 40 | 238 |

The mean survey results reflect the degree of uncertainty associated with each practice. The use of a survey for this economic analysis often required the use of the survey answers from more than one question to assess the impact

[3] *Info*USA is a publicly held company that creates proprietary business databases. Their database includes such information as: Company name, address, phone number, fax number, estimated sales, volume, number of employees, type of business (SIC code or yellow page heading), key contact names, and titles.

of each proposed provision. For example, answers to questions about testing herbals might have been combined with questions about whether the firms manufactured herbals. Some highlights of the survey are:

- Plant characteristics: Manufacturers account for 62 percent of the total firms and 36 percent of manufacturers produce vitamins and minerals as their primary product.
- Use of published good manufacturing practice model: 65 percent of all firms follow some type of good manufacturing practice model, primarily food good manufacturing practices; 28 percent follow the NNFA good manufacturing practices and 31 percent follow FDA's drug good manufacturing practice requirements.
- Personnel: 67 percent of all establishments maintain records of personnel education, training, or experience.
- Quality control: 85 percent of all establishments have a unit or person responsible for quality control. Almost 80 percent of all manufacturers conduct at least some type of identity tests on incoming components and dietary ingredients and 96 percent of these firms also conduct some type of contamination test; 63 percent conduct some type of potency test. Nearly 70 percent conduct tests on inprocess materials or finished products. Of these firms, 97 percent conduct identity tests, 94 percent conduct contamination tests and 72 percent conduct potency tests. Asked whether firms hold reserve samples of each finished batch, 75 percent answered yes. Of the plants that have production processes, 70 percent use production and process controls that identify the points, steps, or stages in the manufacturing process to prevent adulteration. Almost 68 percent of all incoming ingredient or component lots are tested now and almost 70 percent of inprocess or finished product batches are tested in some manner.
- Warehousing: 70 percent of warehouses have temperature controls and 22 percent have humidity controls.
- Consumer complaints: Only 19 percent report incidents to FDA.

5. Baseline Risk

The current number of illnesses caused by poor manufacturing practices requires data linking illnesses directly to poor practices. Without direct evidence on the number of illnesses caused by poor manufacturing practices, we had to use an indirect approach. There are two indirect ways to estimate the number of illnesses caused by defective products:

- We could take the number of reported cases and multiply by a factor to account for underreporting.
- We could take the number of defective products and multiply by the probability of illness for the given defect.

In an ideal analysis, we would estimate the baseline both ways and then compare them. For the analysis of illnesses from poor manufacturing practices, however, we did not have sufficient data to perform either type of baseline estimate.

We looked at many sources for information, including medical and other literature on adverse events, information from poison control centers, reports to the agency, popular newspaper and magazine articles, and surveys of users. The literature review was conducted using Medline, Healthstar, Aidsline, Cancerlit, and OldMedline (Ref. E12). We found evidence of many adverse events associated with dietary supplements. For example, one recent survey found that 12 percent of consumers (about 11.9 million) who have used an herbal remedy claim to have suffered from side effects or other adverse reactions (Ref. E13). The American Association of Poison Control Centers received 6,914 reports on dietary supplements in 1998 (Ref. E14). In a recent survey, 46 percent of respondents answered that people get sick from dietary supplements ''often'' or ''sometimes'' (Ref. E3). In addition, the agency has received many voluntary reports of illnesses caused by dietary supplements (Ref. E15). The vast majority of the illnesses described in the sources we consulted, however, are reported as associated with the ingredients used in the products themselves, not with poor manufacturing processes. We have no direct evidence on what fraction of illnesses can be attributed to manufacturing processes. The anecdotal evidence implies that many illnesses could have been caused by poor manufacturing processes, but with a few exceptions, no evidence explicitly links illnesses to these manufacturing processes.

The agency's recall records are more useful than the reports on illnesses, because the class 1 and class 2 recalls all involve defective products that could have caused illness if ingested. The major public health events that have been linked to poor manufacturing processes show up in the list of dietary supplements recalled. Although the recall data cannot be linked directly to illness data, we have found anecdotes, surveys, and some medical literature on illnesses that could be caused by avoidable manufacturing mistakes. We have recall data that show that manufacturing mistakes exist, so we can construct a possible link between manufacturing mistakes and potential illnesses or injuries. The number of illnesses associated with a recall is both variable and uncertain, and could be anything from zero to quite large. We concluded that one illness would not be an implausibly high average for a recall, so we assumed that a recalled product could be a proxy for a single reported illness associated with a defective product. We ask for comments on this assumption.

Because there are no well established systems for the notification of adverse health events related to dietary supplements, and some significant barriers to reporting, we assume that unreported illnesses caused by poor manufacturing practices are substantially greater than reported illnesses. We relied on Ref. E16 to estimate a more precise relationship between reported and unreported rates. Based on empirical data for drug and vaccine reporting rates among other studies, the author of Ref. E16 determined that for dietary supplements, reported illnesses represent at best approximately 1 percent of total illnesses (Ref. E16). A similar multiplier of 100 linking known cases of foodborne illness to total incidence is often used. We assume that reporting adverse health events due to poorly manufactured dietary supplements would occur at the same proportion as adverse health events caused for other reasons by dietary supplements. We show the sensitivity of benefits to the choice of multiplier below, in the uncertainty and sensitivity analysis of our results.

The outbreak of eosinophilia-myalgia syndrome (EMS) resulting from contaminated L–Tryptophan resulted in the recall of the contaminated products. In part based on this example, we assume that product recalls can indicate when there are adverse health events. We also assume that the reported class 1 and class 2 recalls that have occurred over the last 10 years represent the number and type of recalls that will occur in the future but for the implementation of this regulation. From 1990 through 1999, the agency received reports on an annual average of 13 class 1 and class 2 recalls of dietary supplements. If each recall is a proxy for a reported illness, then the total number of unreported illnesses per year is approximately 1,300. Obviously, to the extent that products are successfully recalled, illnesses will be avoided. Our assumption is that the recall occurs

because at best one person on average has been made ill. We recognize that our procedure generated highly uncertain estimates of the number of illnesses. The use of recalls to estimate reported and unreported illnesses probably generated a distribution of illnesses below the ''true'' distribution, because many illnesses occur that are not linked to recalls and are never reported. We were not able to determine even the approximate size of the underestimation from this procedure.

We estimated the monetary value of the health benefits from CGMP regulations by multiplying the number of illnesses prevented by the health costs associated with an illness. The health benefits associated with preventing an illness come from: (1) Preventing the loss of productivity, (2) the reduction in pain and suffering, and (3) the reduction in expenditures on medical treatment. We measured lost productivity indirectly with measures of functional state, which includes measures of physical function. We estimated the losses caused by pain and suffering with a symptom-problem index. We used direct measures of medical costs, such as payments to physicians and hospitals.[4]

Table 8 of this document contains summaries of our measures of the health effects potentially caused by known instances of defective products associated with poor manufacturing processes. We estimated the health loss per day for the different levels of illness severity by summing the lost productivity (as measured by functional state) and the loss from pain and suffering (as measured by the symptom-problem index[5]). These losses per day can be interpreted as the difference between a day of normal health, where normal is defined as the population's health not affected by these products, and a day of suffering from the health conditions caused by these defective products. The numerical scale is a relative baseline that rests on the notion of a quality-adjusted life day (QALD). The QALD for a day of normal health equals 1; the QALD for death equals 0. The loss of QALDs per illness equals the daily loss multiplied by the number of days the illness lasts. We converted QALDs to dollars by multiplying the index numbers by the value of a statistical life day and adding the direct medical costs.

TABLE 8.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999

| Problem | Class of recall | Number of recalls | Outcomes | Frequency of illness (percent) | Quality adjusted life day | Duration of illness (days) | Medical cost ($) per event | Health cost ($) per event |
|---|---|---|---|---|---|---|---|---|
| Hypervitaminosis A | 1 | 2 | ..... | 100 | 0.472 | 3 | 84 | 936 |
| Salmonella | 1 | 4 | Mild | 93.8 | 0.473 | 2 | 0 | 534 |
| | | | Moderate | 5 | 0.473 | 5 | 800 | 2,223 |
| | | | Severe | 1.2 | 0.563 | 17 | 9,100 | 14,859 |
| | | | Reactive arthritis (short term). | 2 | 0.42 | 25 | 100 | 6,438 |
| | | | Reactive arthritis (long term). | 1 | 0.42 | 5,223 | 400 | 1,320,252 |
| | 2 | 4 | Death | 0.04 | ..... | ..... | 9,100 | 5,009,100 |
| Klebsiella pneumonia | 1 | 1 | Severe | 85 | ..... | ..... | 6,235 | 10,650 |
| | | | Death | 15 | ..... | ..... | 6,235 | 5,006,325 |
| Selenium poisoning | 1 | 1 | Low doses | 50 | 0.482 | 3 | 84 | 954 |
| | | | Severe | 35 | 0.482 | 3 | 2,578 | 4,448 |
| | | | Death | 15 | ..... | ..... | 2,578 | 5,002,578 |
| Stannous fluoride | 1 | 1 | Acute | 100 | 0.473 | 3 | 84 | 938 |
| | 2 | 1 | ..... | ..... | 0.473 | 3 | 84 | 938 |
| Eosinophilia-myalgia syndrome. | 1 | 7 | Mild | 47 | 0.482 | 5,223 | 1,176 | 1,515,863 |
| | | | Moderate | 50 | 0.482 | 60 | 84 | 17,484 |
| | 2 | 41 | Severe | 10 | ..... | ..... | 14,964 | 27,394 |
| Glass fragments | 2 | 1 | Dental injury, simple | 50 | 0.231 | 1 | 139 | ..... |
| | | | Dental injury, complicated. | 12 | ..... | ..... | 3,741 | ..... |
| | | | Oral emergency | 12 | ..... | ..... | 3,741 | 6,428 |
| | | | Tracheo-esophageal obstruction. | 25 | ..... | ..... | ..... | 290 |
| | | | Esophageal perforation. | 1 | ..... | ..... | 14,964 | 23,343 |
| Hypervitaminosis D | 2 | 1 | ..... | 100 | 0.473 | 3 | 168 | 1,022 |
| Pyridoxine (vitamin B6). | 2 | 2 | ..... | 100 | 0.482 | 30 | 168 | 8,868 |
| Super-potent zinc | 2 | 1 | Mild | 50 | ..... | ..... | ..... | 285 |
| | | | Moderate | 40 | ..... | ..... | ..... | 596 |
| | | | Severe | 10 | ..... | ..... | 1,247 | 3,347 |
| Niacin | 2 | 1 | ..... | 100 | ..... | ..... | 84 | 4,258 |
| Yellow #5 (undeclared). | 2 | 5 | Mild allergic reaction | 90 | 0.44 | 2 | 0 | 529 |
| | | | Severe allergic reaction. | 10 | ..... | ..... | 2,494 | 3,346 |

[4] The cost of a hospital day is from the Health Care Financing Agency's Indicator Tables. It is the amount per patient day in 1997, adjusted to 1999 dollars. *See* Ref. E17.

[5] Functional Status Code is a measure of lost mobility (MOB), physical activity (PAC) and social activity (SOC). Lost MOB might mean an inability to drive a car. Lost PAC might mean walking with physical limitations. Lost SOC might mean self-care is not possible. Symptom-problem health utility index is a weighted measure of the cost of each symptom. For example, a sick or upset stomach has a utility weight of .290.

TABLE 8.—SUMMARY OF HEALTH EFFECTS BASED ON POTENTIAL ILLNESS ASSOCIATED WITH RECALLS BETWEEN 1990 AND 1999—Continued

| Problem | Class of recall | Number of recalls | Outcomes | Frequency of illness (percent) | Quality adjusted life day | Duration of illness (days) | Medical cost ($) per event | Health cost ($) per event |
|---|---|---|---|---|---|---|---|---|
| | | | Contact dermatitis .... | 50 | ..... | ..... | 84 | 1,205 |
| Yellow #6, red #40, blue #2 (undeclared). | 2 | 1 | Abdominal cramps .... | 10 | 0.473 | 3 | 84 | 938 |
| | | | Contact dermatitis .... | 90 | ..... | ..... | 84 | 1,205 |
| Copper salts ..... | 2 | 1 | ..... | 100 | 0.473 | 1 | 84 | 369 |
| Digitalis ..... | 1 | 33 | Mild ..... | 94.9 | 0.473 | 3 | 84 | 938 |
| | | | Severe (heart block) | 5 | ..... | ..... | 1,247 | 455,883 |
| | | | Death ..... | 0.1 | ..... | ..... | ..... | 5,000,000 |
| Ephedra (undeclared) | 1 | 1 | Cardiovascular ..... | 14 | ..... | ..... | 1,415 | 3,530 |
| | | | CVS w/chronic ..... | 2 | ..... | ..... | 2,591 | 457,227 |
| | | | Nervous system ..... | 14 | 0.47 | 2 | 1,331 | 1,900 |
| | | | NS w/chronic ..... | 2 | ..... | ..... | 2,507 | 455,597 |
| | | | Liver impairment ..... | 4 | ..... | ..... | 168 | 4,342 |
| | | | Exfoliative dermatitis | 7 | ..... | ..... | 84 | 1,206 |
| | | | Other ..... | 54 | 0.29 | 1 | 0 | 174 |
| | | | Death ..... | 3 | ..... | ..... | 2,507 | 5,002,507 |
| Lactose (undeclared) intolerance. | 2 | 1 | Mild ..... | 100 | 0.48 | 1 | 0 | 290 |
| Iron poisoning ..... | 2 | 1 | Mild ..... | 100 | 0.48 | 1 | 84 | 374 |
| Sulfites (undeclared) | 1 | 1 | Mild allergic reaction | 100 | 0.44 | 2 | 0 | 529 |

We used the transformed value of statistical life to estimate the value of QALD. For the most likely value of a statistical life day, we used $630. We derived this value from a widely-used estimate of the value of a statistical life: $5 million. The $5 million estimate is based on calculations matching labor market risks with wages for risky jobs. Workers in risky jobs tend to receive increased wages to compensate them for (usually) small increases in the probability of death. The implicit value of a statistical life is the increased wage divided by the increased probability of death. The advantage of valuing statistical lives with this method is that it reflects the observed willingness of workers, and by inference, of the whole population of adults, to accept small risks to their lives in a real world risk-dollar tradeoff.

We turn the estimated value of a statistical life into a value of a statistical life day by first assuming that the workers have a remaining life expectancy of 36 years (Ref. E18). Using a 3 percent social rate of time preference, the present value of 36 years is 21.83 years. The social rate of time preference is the average long-term real rate of interest, with no premiums for risk and other factors that affect interest rates. Most analysts use the average real rate on long-term treasury bonds (3 to 5 percent in recent years) to represent the social rate of time preference. The discounted expected days lost for a statistical death is 21.83 x 365 = 7,968. Therefore, the value of a statistical day is $5 million/7,968, which is approximately $630. We use this value to estimate the public health benefits from preventing illness.

In addition to lost productivity and pain and suffering, illness caused by supplement contamination leads to direct medical costs. Direct medical costs include the cost of medicine, hospitalization, and visits to physicians and other professionals. We included all estimated medical costs, not just out-of-pocket expenses. These full medical costs often are missed because most medical care is covered by health insurance that separates the bearer of the medical cost (society) from the bearer of the utility losses (the ill person).

The total costs of illnesses caused by the contamination of dietary supplements from poor manufacturing practices would be the costs per illness (classified by severity) multiplied by the number of illnesses (classified by severity). For chronic illnesses, the utility losses and medical costs stretch indefinitely into the future. We used a real discount rate of 7 percent to calculate the present value of chronic medical expenditures and utility losses. OMB suggests using a real discount rate of 7 percent to analyze the costs and benefits of regulations. This rate approximates the marginal rate of return on an average investment in the private sector in recent years. We used a different discount rate for the social rate of time preference (3 percent) and the discount rate of future medical costs (7 percent). Medical costs, like all expenditures, reflect the foregone benefits from alternative investments. The pure social rate of time preference can differ from the return on private investments.

6. Benefits and Costs

Changes in current practices by manufacturers, or consumers, or both, cause incremental (marginal) benefits and costs. There are several possible reactions manufacturers might have to the proposed regulatory requirements:

- Stop producing dietary supplements and possibly go out of business.
- Move production to a foreign country where compliance with these regulations is more difficult to enforce.
- Comply with part or all of the proposed regulation. Consumers will likely be confronted with higher priced dietary supplements but also products that are, on average, more uniform and higher quality. To the extent that the latter is unknown to consumers, they will probably reduce consumption of dietary supplements, perhaps in some cases substituting them with alternative products such as foods.

The benefits from the proposed regulation and the regulatory options result from reducing contamination and adopting practices that will result in consistently high quality dietary supplements. Creating industry-wide minimum requirements for good manufacturing practices should reduce the occurrence of product defects, which in turn should reduce the number of illnesses and deaths.

Defective products can cause isolated cases of illnesses, but also rare catastrophic events such as the outbreak of eosinophilia myalgia syndrome (EMS) that resulted from the consumption of contaminated L-Tryptophan. That outbreak caused 38 deaths and over 1,500 illnesses.

The provisions that require establishments to maintain consumer complaint files related to manufacturing practices will generate additional health benefits. The use of these files by manufacturers and the agency will help identify dietary supplements that were manufactured or contaminated in ways that could cause a significant or unreasonable risk of illness or injury. These records may reduce the likelihood of catastrophic events, because a cluster of illness complaints could be identified, and preventive action taken before the number of illnesses reached catastrophic levels.

Improved product quality will also reduce the number of products recalled. Certain manufacturing practices, such as more frequent finished product quality testing, help establishments to identify problems before the products are released for consumption. If defective products are caught before they are released, they will not be recalled.

Creating minimum requirements should also generate benefits for consumers by reducing the variation in product quality. Creating verifiable minimum manufacturing requirements reduces the private effort necessary to distinguish products manufactured, packaged, and held using good practices from those using poor practices. Reducing the effort needed to find products with the identity, purity, strength, quality, and composition, among other characteristics, creates a potentially substantial, though implicit, benefit for consumers.

The benefits from the proposed rule, then, are from:

- Reduced health costs caused by the reduced number of illness;
- Fewer product recalls, and;
- Greater assurance of consistent and better quality products.

a. *Reduced illnesses.* The proposed regulation would improve the safety of dietary supplements, which would reduce the number of illnesses and the probability of deaths caused by manufacturing problems. The proposed rule would also improve product safety through the provisions requiring records and investigations of consumer complaints related to manufacturing practices. We assumed that the proposed rule would reduce both sporadic illnesses and catastrophic outbreaks. We estimated the reduction of sporadic or annual illnesses by using the agency's recall records as evidence of possible illnesses; class 1 and class 2 recalls of dietary supplements all involved adulterated products that could have caused illness if ingested. We estimated the reduction of illnesses from preventing catastrophic events by using the public health effects of the outbreak of EMS that resulted from consumption of contaminated L-Tryptophan.

i. *Reduced illnesses estimated from recall data.* For annual illnesses, we used this formula for estimating the benefits from fewer illnesses:

*Marginal health benefits = baseline (or current) number of illnesses caused by poor manufacturing practices × expected reduction in the number of illnesses brought about by the proposed regulation × health cost saved per prevented illness.*

We estimated the annual expected health benefits for the proposed rule by taking the values in table 8 of this document and weighing them by their incidence in the table. We computed the expected health benefits from preventing a single illness (of any type) associated with a class 1 recall as a weighted average of all potential illnesses (see table 8 of this document), with the potential illness divided by the total number of class recalls.

The following formulas show how we calculated the average health benefits of preventing a single illness associated with a class 1 recall.

$\$health_{ij} = (QALD \times days \times \$ \text{ per } QALD)_{ij} + \$ \text{ medical}_{ij}$

$EB_j = \Sigma_i (f_{ij} \times \$health_{ij})$

$EB\ [c1] = \Sigma_j (w_j \times EB_j)$

$w_j = r_j/(\Sigma_j r_j)$

Where:

$\$health_{ij}$ = health costs of severity level i of illness j;

QALD = quality adjusted life day;

$ per QALD = dollar value of a statistical day;

$ medical = direct medical costs;

$Eb_j$ = expected health benefit from preventing a single case of illness j;

$f_{ij}$ = frequency of severity i of illness j ($\Sigma f_{ij} = 1$);

m = number of levels severity for illness j;

EB [c1], EB [c2] = expected benefits from preventing an average illness associated with a class 1 recall or a class 2 recall;

$w_j$ = weight of illness j;

$r_j$ = number of product recalls for hazard j;

n = number of hazards or potential types of illness.

We then repeated the procedure for class 2 recalls and the associated illnesses in table 8 of this document. Table 9 of this document shows the average value of preventing a single illness associated with class 1 and class 2 recalls.

We estimated the annual marginal health benefits as the health benefits per illness for each class of recall multiplied by the estimated number of recalls.

*Health Benefits = (EB[c1] × estimated annual number of class 1 illnesses prevented) + (EB[c2] × estimated annual number of class 2 illnesses prevented).*

To estimate the number of illnesses prevented, we started with the average annual number of products recalled for the decade 1990 to 1999—six class 1 and seven class 2. As discussed above, we then assumed that these recalled products represented proxies for about 1 percent of all illnesses caused by these problems leading to the recalls. With that assumption, we get 600 illnesses from class 1 recalls and 700 illnesses from class 2 recalls (see table 9 of this document).[6]

Table 9 of this document shows the estimated value of the health benefits from the proposed rule using class 1 and 2 recall data.

TABLE 9.—HEALTH BENEFITS USING RECALL DATA

| | |
|---|---|
| Total number of illnesses prevented, recall base | 1,300 |
| Total number of illnesses associated with class 1 recalls | 600 |
| Total number of illnesses associated with class 2 recalls | 700 |

[6] We used a probability distribution to represent the uncertainty associated with the number of illnesses. We modeled the number of illnesses prevented for each class as the average number of recalled products plus a negative binomial distribution representing unknown cases. The negative binomial distribution estimates the number of failures (unknown cases) that will occur before some number of successes (known cases) for a given probability of success. In the negative binomial distribution, we assumed that the number of recalled products were reported cases and that the probability of reporting equaled 1 percent (Ref. E16). The result is that the mean estimated number of illnesses is 100 times the reported number of recalls.

TABLE 9.—HEALTH BENEFITS USING RECALL DATA—Continued

| | |
|---|---|
| Dollar estimate of health benefit for preventing an illness associated with a class 1 recall | $60,000 |
| Dollar estimate of health benefit for preventing an illness associated with a class 2 recall | $5,000 |
| Dollar estimate of annual health benefits, recall base (million) | $39 |

ii. *Health benefits from preventing a rare catastrophic event.* We estimated the marginal health benefits from reducing the probability of a catastrophic event as follows:

*Marginal health benefits = Change in probability of rare catastrophic event caused by poor manufacturing practices brought about by the proposed regulation × the number of illnesses caused by the rare event × health cost saved per illness.*

In 1989, there was a widespread outbreak of EMS resulting from consumption of contaminated L-Tryptophan. More than 1,500 cases (175 acute illnesses and 1,287 chronic illnesses) and 38 deaths were identified in 50 states (Refs. E21 and E22). The outbreak prompted a recall of all dietary supplements that contained more than 100 mg per daily dose, which later was expanded to almost all products containing L-Tryptophan. We used the public health cost of this event as an estimate of the cost of a future rare catastrophic event associated with dietary supplements.

EMS is characterized by severe myalgia and elevated eosinophils counts. Some of the most common symptoms are fatigue, weakness, fever, and arthralgia. Although a repeat of the EMS outbreak is not expected, it is an example of the rare, catastrophic events that should be prevented or mitigated by the proposed CGMP regulation. The testing provisions of the proposed regulation should reduce the probability that contaminated ingredients would be released to the public. The provisions for keeping complaint files and investigating complaints would allow more rapid identification of a major health event; the defective products could be identified and withdrawn well before the event claimed as many victims as L-Tryptophan.

To estimate the benefits from preventing reduction in the probability of a rare catastrophic event occurring, we first estimated the period between now and the last rare catastrophic event, 1989, and we needed to make baseline assumptions about the likely time interval between events. The last catastrophic event occurred over 13 years ago, so we assumed that the lower bound would be 50 years. For lack of data, we then assumed a uniform probability distribution between these two bounds, which leads to a rough estimate of once in 30 years. We do not know how likely rare events are, nor do we actually know the likelihood of reducing these events by the proposed regulation. There can be no conclusive empirical support for the likelihood of a future event because the past may not predict the future in the absence of a stable frequency distribution that reflects a statistically significant number of similar events. All we know is that such an event occurred at least once in the recent past, and remains a possibility. We recognize that our lack of information about such events creates significant uncertainty about the social costs of these events and the health benefits from reducing their impact. Our estimate is meant to convey the potential or hypothetical enormity of such an event, not the certainty of such an event. We would like comments regarding our estimate of such an event.

The health cost of the EMS outbreak was large because of the number, severity, and duration of the cases. One followup study (Ref. E21) found 88 percent of EMS patients were still symptomatic 21 to 64 months after onset. The symptoms associated with EMS also frequently lead to activity limitations. Another study of victims (Ref. E22) found that 74 percent of symptomatic EMS sufferers were limited in their functions 12 months after the onset of illness.

To find the health cost of the outbreak, we estimated the cost of the following health outcomes: Death, acute illness only, chronic illness with no activity limitation, chronic illness with mild activity limitation, chronic illness with moderate limitation, and chronic illness with severe limitations. To determine the cost for each of these health outcomes, we multiplied the lost quality-adjusted life days over the duration of the illness by the value of a life day. For medical costs, we estimated the cost of hospitalization for the EMS patients who required hospitalization (32 percent of all victims), by assuming 3 days per hospital stay. We used $1,284 as the cost per day of time spent in a hospital (Ref. E17). We assumed that chronic sufferers visited the doctor once a year at a cost of $84 per visit. We estimated the total cost of the event to be about $2 billion. Most of the cost of the outbreak comes from the deaths and severe chronic illnesses. Table 10 of this document shows the values used in the calculation. Note that the categories are not mutually exclusive. The average age of victims was about 50, so the value of statistical life was adjusted accordingly. If the event occurs about once in 30 years in the absence of the proposed rule, then the expected average annual cost would be about $66 million.

TABLE 10.—HEALTH BENEFITS FROM PREVENTING RARE CATASTROPHIC EVENT

| | Number | Costs per case |
|---|---|---|
| Hospitalization | 480 | $3,741 |
| Death | 38 | 4,214,301 |
| Acute Illness | 175 | 8,760 |
| Chronic illness not limited | 380 | 1,091,849 |
| Mild chronic illness, limited | 190 | 1,349,002 |
| Moderate chronic illness, limited | 307 | 1,601,539 |
| Severe chronic illness, limited | 409 | 1,602,844 |
| Visits to physicians | 1,287 | 1,539 |

The benefits attributable to this proposed rule from preventing a rare catastrophic event are highly uncertain. We do not know if such an event would, in the absence of the proposed regulation, ever occur again. The EMS outbreak may have been a unique event, although the recent severe public health effects associated with aristolochic acid in Europe show that such similar events remain possible (Ref. E23). We also do not know that if another catastrophic event occurred, the health effects would be as large as for L-Tryptophan. Some of the smaller clusters associated with dietary supplements could represent small events potentially prevented by the proposed CGMP regulations (Ref. E15).

We included reducing the likelihood of a catastrophic public health event as a benefit of the rule because the battery of checks and controls that would be required under the proposed regulation would reduce the likelihood of such an event occurring again. In particular, the requirement that establishments keep records of consumer complaints should lead to early identification and prevention of potential catastrophic events related to manufacturing practices.

Our estimate of the health benefits associated with this proposal is based on two models that estimate future illnesses and deaths prevented by this proposed rule: Illnesses caused by sporadically adulterated products and predicted by recall data; and rare catastrophic outbreaks of illnesses, as predicted by one previous event in the United States and corroborated by one in Europe. The frequency and magnitude of a rare catastrophic event is largely hypothetical. In contrast, sporadic illnesses are small but frequent events that happen routinely. Small sporadic events are characterized by significant underreporting primarily because of the difficulty linking an illness with the cause of an illness. Determining the cause of an illness in small sporadic events is made even more difficult because only the most serious illnesses are likely to be reported and because of the difficulty of linking the cause of an illness with poor manufacturing practices. Catastrophes are large but infrequent events that create hundreds of illnesses with reporting that is close to complete because the public health system typically devotes considerable care in identifying the origin and magnitude of the problem. Adding these two models should not lead to double counting the health benefits. Double counting would most likely occur if a recalled product caused both sporadic illnesses and a catastrophic number of illnesses and the public health system accurately recorded the full number of both sporadic and catastrophic illnesses.

b. *Fewer products recalled.* Implementation of the proposed regulation would reduce the number of adulterated products distributed to the public, which would reduce the number of products recalled. Manufacturing practices, such as testing of finished products and better recordkeeping, will increase the ability of establishments to identify problems before products are released for distribution. If adulterated products are caught before they are distributed, they will not be recalled.

To estimate the direct benefits from fewer recalled adulterated dietary supplements, we estimated the baseline number of annual recalls of dietary supplements due to contamination before the proposed regulation. From 1990 to 1999, FDA received reports on an average of 20 recalls per year (Ref. E12). The average figure reported here includes class 3 recalls. The number of units of dietary supplements for each recalled product varied, so we used a distribution per recalled product of 1,000 units to 34,000 units (Ref. E12). Product price also varied, with most prices falling between $5 per unit and $9 per unit; we used a most likely price of $7.70 per unit. We also included an adjustment for the goodwill lost by the establishment as a result of the recall. Studies of changes in market valuations of firms after recalls indicate that the value of lost customer goodwill, based on the decline of the share price of publicly traded stocks from recalls is often as large as the cost of the recall itself (Ref. E24). We multiplied the direct cost of the recall by two in order to include the lost goodwill. The result is an estimated savings of about $3 million per year.

We based the estimated benefits from fewer recalled products on our recall data. If there were private recalls due to contaminated supplements that were not included in our data, the benefits from reduced recalls may be understated.

c. *Reduced hypothetical search costs as a measure of the benefit from increased assurance of quality.* Consumers incur a cost if they purchase products but do not get the quality of product they anticipated. Determining the cost they incur is difficult, because we cannot look at the price of poor quality products and conclude that consumers paid too much, even when they did not get the quality they anticipated. We cannot disentangle the price consumers are paying, from the price they should be paying, because we assume consumers expect some unknown number of their products may not meet their expectations but purchase them anyway. In other words, we cannot rule out the possibility that the purchase price already incorporates the expectations of consumers that some products will be ''lemons.'' Because we cannot look into the minds of consumers to determine their expectations or their willingness to pay for these products, we can only estimate the benefits from more uniform quality by estimating the changes in behavior that would occur if consumers were aware of the change in quality brought about by the proposed rule. In other words, we assume that if the quality attributes of dietary supplements were observable, then consumers would spend time searching for those attributes, as they do for other goods. We measured this benefit as a reduction in the hypothetical search costs for product quality, meaning the identity, quality, purity, strength, and composition claimed on the label.

The hypothetical measure of quality starts by assuming the existence of a baseline amount of search necessitated by the existence of poor manufacturing practices. Our hypothetical consumers must search for products made with good manufacturing practices, because they cannot take such practices for granted when purchasing dietary supplements. Although the search we use as a measure of the benefits from improved quality is hypothetical, the values we use in estimating our search model are based on data and inferences about real searches for other products.

To get the products they want, people search across the range of market alternatives. Several recent articles have noted the large variation in product quality for different goods and services (Refs. E25, E26, and E27). Searching takes time and resources that could be used for other purposes, so a regulation that reduces search provides measurable benefits to consumers. To reduce the effort devoted to searching, consumers of dietary supplements should therefore be willing to pay some amount. We lack, however, a measure of what they would be willing to pay, partly because some consumers may not know that dietary supplements may contain more or less (or something not even expected) of what they think they are buying. Indeed, if consumers of dietary supplements could determine the quality of these products by merely examining the product or the label, the market alone would be sufficient to ensure that firms responded to consumer preferences for product quality. Consumers would search for those brands that are more

likely to have the desired quality, and manufacturers would most likely adopt sufficient quality controls to satisfy consumer preferences. The market response is weak now because only some consumers know that product quality problems exist, and even these consumers must rely on imperfect information. If there were uniform quality control practices throughout the industry that ensured against product quality defects, consumers would not have to search for the products that they believe are free from contamination or have the identity, purity, strength, quality, and composition they want. Consumers could more reasonably assume that all products are free from contamination and have the identity, purity, strength, quality, and composition stated on the label.

We faced the problem of trying to measure what people would pay for more uniform products quality if they knew that manufacturing quality requirements did not already exist. To estimate what people would pay, we start with the hypothetical behavior of people aware of the lack of uniform product quality; we call these hypothetical people the ''sophisticated consumers.''

Sophisticated consumers spend time searching for signals about the quality of dietary supplements. The proposed CGMP regulations would reduce the amount of search (by some uncertain amount) carried out by these consumers. The benefits of the rule, however, would not be confined to sophisticated consumers. We also expect ''naive consumers'' to enjoy the benefits. Naive consumers would incur the costs of additional search once the correct or adverse information about quality is available, suffer from worry or an illness from taking poor quality products, or incur the cost of paying for products that do not meet their needs (Ref. E28). Once good practices are in place they would avoid these costs. Naive consumers are those who fail to search for quality or search little not because they do not care but because they do not know that quality varies as much as it does. In other words, they lack the information that problems exist; if they know about the problems, they would search or be willing to pay more to ensure that supplements they consume meet minimum quality standards. Although these naive consumers may not change their behavior in response to the proposed CGMP regulation, they would nonetheless enjoy the benefits. The naive consumers, of course, also represent real consumers of dietary supplements. The total benefits of the quality standards part of the proposed rule will be the implicit value of the gain in product quality enjoyed by all consumers.

The problem is to measure that gain based on hypothetical searches. We needed to use data from searches in other markets, because we found no information on direct or indirect searching for minimum dietary supplement quality standards. For the sophisticated consumer, we assumed that the value of search time should be approximately the same as the willingness to pay for an attribute of the good. Sophisticated consumers will hypothetically search until the expected benefit of continued searching is less than the expected cost of continued searching. The total cost of search time will, on average, be no more than the expected cost of the additional quality desired. Search time includes the time spent: Reading product labels and other literature about the product, comparing one product with other products, examining the product itself (sometimes carefully), thinking about the product, and second guessing final decisions. It might also include the time actually shopping for the product: Finding the locations where the product is sold, driving there and back, waiting in checkout lines, and walking up and down the aisles.

We used information on shopping times for a range of products to derive an estimate for the hypothetical search time for dietary supplements. We assumed that some fraction of shopping time is pure search time, although we also recognize that search time includes more than the search for product quality. Some search time, for example, is for price, efficacy, and other attributes. The reduction in search time for the sophisticated consumer would therefore be at most a fraction of total search time for dietary supplements. The measure of time saved then is:

Reduced search time due to CGMP regulation = shopping time × fraction of shopping time spent searching × fraction of search time associated with searches for quality × fraction of search time associated with searches for quality that would be eliminated if CGMP rule guaranteed minimum quality.

We took the estimated reduction in hypothetical search time for the sophisticated consumer and applied it to all consumers to get an estimate of the implicit benefits of establishing minimum quality standards. This estimated saving in hypothetical search time is not a forecast of reduced shopping time; it is a proxy measure of the benefit from reduced variance and improved mean product quality. We anticipate little or no change in aggregate shopping time for dietary supplements.

We converted the time measure into a monetary measure by multiplying the time reduction for sophisticated consumers by the average wage rate. The benefits measure reduced search time associated with improved quality assurance:

Quality assurance benefits = reduction in search time (in hours per year) per sophisticated consumer × average wage rate per hour × total number of consumers.

The shopping time model is an indirect approach to measuring benefits in a market with asymmetric information; it is not a prediction about how shopping behavior will change in that market. Indeed, we believe that most of the beneficiaries of this part of the rule will never recognize that they are beneficiaries.

Standardization imposes minimum requirements on manufacturing, which in turn should reduce the variance of product quality. The reduction in product quality variation should reduce the amount of information sophisticated consumers need to acquire before purchasing dietary supplements (Ref. E29). People need not rely as much on such indicators as brand names, price, place of purchase, articles in consumer magazines, or advertising to determine the likelihood that dietary supplements meet minimum quality standards.

Although no studies deal with dietary supplements directly, the literature on consumer search for other commodities provides insights that increase our understanding of the search costs for supplements (Refs. E30 and E31). Duncan and Olshavsky (Ref. E32) surveyed buyers of television sets and found that 88 percent of respondents performed some type of search activity before purchase. In a study (Ref. E33) of consumer search for microwave ovens, the average buyer of a new microwave oven was willing to search for four alternative products. Search for groceries has been characterized as a two-stage process (Ref. E34). First, people engage in prestore activities, such as reading advertisements, writing shopping lists, clipping coupons, and comparing stores. Second, people engage in search activities at the store, including price and product comparison and search for items with coupons. Most people devote time to search activities for all but the most routine purchases.

To estimate the reduction in hypothetical search costs from the proposed rule, we started with estimates

of the time consumers spend in search for groceries and other household purchases (including durable goods). We assumed that the search time for these products was related to shopping time. Because search costs include the costs of evaluating magazine articles or brochures, the costs of obtaining a friend's advice, and the costs of instore product comparisons, our estimates will not correspond precisely to the actual costs of search for these products (Ref. E35). We believe, however, that the measure will be a reasonable approximation. Although search time often takes place outside of measured shopping time, measuring search time as some proportion of total shopping time should generate a plausible if not a precise estimate.

We generated three models of search time for dietary supplements, based on three separate studies of shopping time:

- Drug Store.
- Use of Time.
- Grocery Store.

We used three models based on different assumptions because using a range of studies reduced the likelihood of systematic bias in our analysis.

*The drug store model.* The drug store study recorded the amount of time people spent looking at an item on the shelf before making a purchase (Ref. E36). Customers, on average, spent 3.75 minutes studying a product before purchasing it. Although there are quality standards in place for over-the-counter drugs and not for dietary supplements, we assumed that this represented a measure of the amount of time the sophisticated consumer might spend searching for a product with the desired quality.

*The use of time model.* The Americans' Use of Time Project (Ref. E37) used time diaries to study how adults spent all of their time. The study collected data from over 3,500 adults on use of time. Data from these time diaries reveal that adult Americans spent about 364 minutes per week shopping for personal consumption items, such as groceries and other household products.

*The grocery store model.* In the grocery store study, hidden observers tracked and recorded shopping time in the store (Ref. E38). The study found that people on average spent about 21 minutes shopping in the grocery store. By combining estimated time per trip with the Food Marketing Institute's (Ref. E10) finding that consumers average about 2.2 grocery shopping trips per week, we generated an estimate of search time for all grocery store purchases of 46.2 (= $2.2 \times 21$) minutes per week.

For each of the models, we needed to make assumptions to convert shopping time for other commodities into search time for dietary supplements. Table 11 of this document shows the assumptions and information used in each model.

TABLE 11.—THREE MODELS OF SEARCH TIME: ASSUMPTIONS USED IN SIMULATIONS

| Variable | Value or distribution | Source and notes |
|---|---|---|
| **Drug Store Model** | | |
| Search time in minutes per item | 3.75 | Ref. E30. |
| Number of products per person per year | 6.57 | Ref. E4. |
| Average wage rate | $15.65 per hour, or $0.26 per minute | Ref. E42. |
| Population | 273 million | Ref. E19. |
| Fraction of search time devoted to searching for quality. | 0.2 (based on uniform distribution, 0.1 to 0.3) | Based on number of attributes consumers search for. |
| **Use of Time Model** | | |
| Weekly shopping time for all items in minutes | 346 | Ref. E37. |
| Fraction percent of budget spent on supplements. | $15.5 billion/$6,250 billion | Ref. E4 and E19. |
| Average wage rate | $15.65 per hour, or $0.26 per minute | Ref. E42. |
| Adult population | 205 million | Ref. E19. |
| Ratio of search time to shopping time | 0.7 (based on uniform distribution, 0.4 to 1.0) | Based on descriptions of shopper behavior. |
| Fraction of search time devoted to searching for quality. | 0.2 (based on uniform distribution 0.1 to 3.0) | Based on number of attributes consumers search for. |
| Potential reduction in search time attributable to CGMP regulations. | 33% most likely (could be between 15 and 50%). | Based on likelihood of problem and likelihood that search will decline proportionally, and the expert opinion of pharmacists. |
| **Grocery Store Model** | | |
| Weekly shopping time for groceries in minutes | 46.2 | Ref. E38. |
| Ratio of supplement expenditures to grocery expenditures. | $15.5 billion/$710 billion | Ref. E38. |
| Average wage rate | $15.65 per hour, or $0.26 per minute | Refs. E4 and E19. |
| Adult population | 205 million | Ref. E19. |
| Ratio of search time to shopping time | 0.7 (based on uniform distribution, 0.4 to 1.0) | Based on descriptions of shopper behavior. |
| Fraction of search time devoted to searching for quality. | 0.2 (based on uniform distribution, 0.1 to 0.3) | Based on the number of attributes that consumers search for. |
| Potential reduction in search time attributable to CGMP regulations. | 33% most likely (could be between 1% and 50%). | Based on likelihood of problem, the likelihood that search will decline proportionally, and the expert opinion of pharmacists. |

The drug store data generated a direct estimate of search time. In the drug store model we assumed that the time spent standing in front of the drug product could be used to estimate the time searching for dietary supplements. We then used data on the number of products purchased per person and the total U.S. population to generate an estimate of annual search time for dietary supplements.

To estimate the time spent searching for supplements from the use-of-time study, we assumed that the share of all shopping time devoted to supplements would be proportional to the share of a consumer's budget spent on supplements. We recognize that it could well be higher if supplements require more search than the average commodity. According to an industry source and FDA projections, consumers spent about $15.5 billion on dietary supplements in 1999 (see table 5 of this document). Consumers spent about $6,250 billion on all personal consumption in 1999, which means that dietary supplements accounted for about 0.24 percent of those expenditures. Personal consumption expenditures included in this estimate are food, alcoholic beverages, housekeeping supplies (such as laundry and postage), household furnishings and equipment (such as furniture and appliances), apparel (includes footwear), personal care products and services, reading materials, tobacco products, and smoking supplies. Annual shopping time per person for dietary supplements would therefore be about 44.6 minutes per year (= ($15.5 billion/$6,250 billion) × 346 minutes per week × 52 weeks). We converted shopping time to search time by assuming that search time equaled 40 to 100 percent of shopping time. Total search time equaled search time per adult multiplied by 205 million adults. We assumed that all adults would perform search, although we recognize that not all adults consume dietary supplements and not all search is conducted by adults. Children might search for these products also. The opportunity cost for children, as measured by their wage rate is much less than for adults, so we assumed their search time could be ignored. We used the total adult population rather than just the adult consumers of dietary supplements, because the shopping time studies are for all adults.

We estimated search time in the grocery store model with assumptions similar to those in the use-of-time model. We assumed that the ratio of search time for supplements to search time for groceries would equal the ratio of expenditures on supplements to expenditures on groceries. Estimates from the 1998 Consumer Expenditure Survey (Ref. E39) (adjusted for changes in prices between 1998 and 1999) reveal that consumers spent approximately $710 billion on grocery store purchases in 1999. Grocery store purchases included food, alcoholic beverages, housekeeping supplies, personal care products, tobacco products, and smoking supplies. Annual shopping time per person for dietary supplements would therefore be about 52.5 minutes per year (= ($15.5 billion/$710 billion) × 46.2 minutes per week × 52 weeks). We again converted shopping time to search time by assuming that search time equaled 40 to 100 percent of shopping time. Like the estimate from the use of time model, this value was then multiplied by 205 million adults.

We used these three models based on different assumptions because we wanted to explore a range of studies to avoid systematic bias in our analysis. We recognize that the three estimated annual search times for dietary supplements do not represent the search for quality alone. Consumers search for a variety of features; only part of every search will be devoted to quality. We assumed that 10 to 30 percent of pure search time involves quality searches. Estimating the impact of CGMP regulations on consumers' search time is difficult, since no previous studies have analyzed the changes in search time following the adoption of CGMP regulations or from increases in product quality standardization. However, a consistent finding from the literature is that search time should decline following a decrease in the variation in product quality (Refs. E35 and E40). In the absence of previous empirical studies, we assumed that the proposed rule would reduce the hypothetical search time for quality ''the search time of sophisticated consumers'' by 1 to 50 percent, with 33 percent the most likely value. A survey of pharmacists reported their belief that 30 percent of their customers place manufacturing quality as a top priority in selecting one herbal over another (Ref. E41). We also used evidence from product tests that indicated that up to 33 percent of products were missing key ingredients or contained unwanted ingredients (Refs. E25, E26, and E27). If the proposed rule guarantees that products will contain what the label claims, then perhaps search time for quality will decline by that percentage.

To estimate the value of the possible reduction in searching for quality, we multiplied our estimated time saving by the average wage rate, which is an estimate of the value of time. The average hourly wage rate for U.S. workers was $15.65.[7] We ran computer simulations of all three models. The results for the three models are shown in table 11 of this document.

[7] Personnel Employment, Hours, and Earnings. Series ID: EES00510006 Seasonally Adjusted, Industry: Goods-producing Data Type: Average hourly earnings of production workers, Employment Cost Index, Bureau of Labor Statistics.

d. *Other benefits.* The proposed regulation could also reduce the total time and effort that all covered establishments expend to monitor ingredient suppliers and holders of their products. Because all ingredients and holders would be subject to the same uniform minimum requirements, variation in their practices would decline, so firm monitoring of upstream and downstream vendors could decline.

The provision that requires establishments to maintain complaints files would allow a manufacturer to more readily be able to identify a product that causes a significant or unreasonable risk of illness or injury. The manufacturer can then take necessary steps to prevent any additional adverse health impact. We have attempted to quantify this benefit for preventing catastrophic events, but not for reducing smaller risks. FDA adverse event reports, however, imply that many such small events occur, and the proposed rule could prevent some of them (Ref. E15).

In addition, if the same adverse events show up in complaints received by different firms selling products with the same or similar manufacturing problems, no one firm selling such products may recognize the need to investigate the complaints especially if the risk is relatively low. Because we would have access to complaint files, our review would be more likely than any individual firm's review to identify the need to investigate the complaint because of a reasonable possibility of a relationship between the manufacturing process of a dietary supplement and the adverse event.

e. *Total measured benefits.* The total measured benefits from the proposed rule are the sum of the value of health benefits, the value of the reduced number of product recalls, and the reduction in hypothetical search costs. Table 13 of this document shows the total benefits.

TABLE 12.—THREE MODELS TO ESTIMATED SEARCH COST SAVINGS

| Baseline model | Cost savings (in millions) |
|---|---|
| Drug store model | $108 |
| Use of time model | 101 |
| Grocery store model | 119 |
| Average of three baseline models | 109 |

TABLE 13.—SUMMARY OF ANNUAL BENEFITS

| Benefits | Mean (in millions) |
|---|---|
| Fewer illnesses (from table 8) | $39 |
| Fewer illnesses (from table 10) | 66 |
| Fewer product recalls (from table 9) | 3 |
| Reduced consumer search (from table 12) | 109 |
| Total benefits | 218 |

7. Costs

The same changes in practices that produce benefits also have costs, the opportunity costs of not doing what consumers and manufacturers are now doing. The proposed regulation would require dietary supplement establishments to adopt some new practices in order to manufacture, package, and hold their products. The costs incurred for those who choose to comply will be for personnel, grounds and physical plant, equipment and instrumentation controls, quality control and laboratory operations, production and process controls, handling consumer complaints, and holding. In some cases, establishments would need to make capital improvements to the physical plant, add or replace equipment or controls, perform additional maintenance, keep records, carry out tests, or execute a variety of additional tasks that they may not have previously performed. We estimated the additional costs of production associated with the proposed rule and the leading regulatory options, using the survey (Ref. E2) to estimate baseline manufacturing practices.

a. *Description of the costs.* To estimate costs for the dietary supplement industry, we initially divided the industry into four product categories and three size categories. Because the survey showed that there were only a few establishments in some categories, we consolidated the size and product into three size categories. The size categories were:

- Very small (fewer than 20 employees).
- Small (20 to 499 employees).
- Large (500 or more).

Although this consolidation glosses over the important differences across products, the purpose is to estimate the broad average costs of the rule.

For each category, we constructed a cost model that included every provision of the CGMP regulations that the proposed rule requires or recommends. We then attached a cost to each provision that had an activity associated with it. Most provisions did not have costs attached to them, mainly because they were either descriptive or the costs were included elsewhere. For the rule as a whole, we estimated the marginal, or additional costs for over 70 provisions of the proposed rule.

We expressed the cost as cost per unit, with the unit being either the establishment, the number of employees, or the annual number of batches produced. The costs of this proposed rule included the following general activities: Sanitation, production and process controls, holding and distributing, and consumer complaints.

b. *Costs of general activities.* i. *Sanitation.* Sanitation includes both one-time capital improvements and ongoing efforts. Some provisions of the proposed regulation may require establishments to perform one-time capital improvements to their physical plant facilities.

The proposed regulation would also require, if not already in place, physical plant owners to install new or additional plumbing systems to carry additional water or sewage, additional toilet or hand washing facilities, additional facilities for trash disposal, or new signs to instruct employees. The proposed regulations might also require establishments to add space in order to keep equipment and materials farther apart, which will help to prevent contamination or mixups. Other possible capital expenditures (among many other possible requirements) include:

- Replacing floors, walls, or ceilings with smooth, hard surfaces;
- Changing fixtures, ducts, or pipes that might be a source of contamination by dripping or condensation;
- Adopting ventilation control systems including filters, fans, or other air-blowing equipment to prevent odors or vapors;
- Additional lighting to ensure that equipment, contact surfaces, or other areas where supplements are examined, processed, or held can be adequately seen.

Sanitation also requires that equipment utensils must be of suitable design, construction, and workmanship to enable them to be adequately cleaned and maintained. To meet this requirement, some establishments may need to provide additional maintenance or additional cleaning and sanitation for their equipment and utensils. Also, freezers and cold storage compartments used to slow or arrest the growth of microorganisms must be fitted with thermometers to accurately show the temperature within the compartments. Instruments and devices used in manufacturing must be accurate, adequately maintained, and adequate in number. To meet this requirement establishments might have to purchase new equipment, replace old equipment, or provide additional maintenance to existing equipment.

ii. *Production and process controls.* Production and process controls are the main preventive mechanism to ensure the identity, purity, quality, strength, and composition in the proposed rule. Establishments must implement a system of production and process controls that covers all stages of processing, from the receipt and acceptance of components, dietary ingredients, dietary supplements, packaging, and labels through the release for distribution and holding of the dietary ingredients and dietary supplements. Establishments must identify points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. Establishments must also establish specifications for the identity, quality, purity, strength, and composition of components, dietary ingredients, or dietary supplements. Establishments must monitor the points, steps, or stages in the batch production, as specified in the master manufacturing record, where control is necessary to prevent adulteration. Establishments must establish specifications for packaging to ensure that containers or closures that come into contact with dietary ingredients or dietary supplements are not reactive or absorptive and are composed of substances that are safe for use in or on food.

Establishments that have not already done so must establish a quality control unit with one or more individuals that have with the authority and responsibility to review the results of monitoring, make decisions on the disposition of materials, and identify whether actions taken to correct any deviations are appropriate. The quality control operation must ensure that components, dietary ingredients, and dietary supplements conform to specifications.

iii. *Holding and distributing.* Establishments must hold and distribute dietary ingredients and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, quality, purity, strength, and composition of the dietary ingredients and dietary supplements are not affected. Establishments must also identify and

hold components, in-process materials, and dietary supplements under conditions that will protect them against mixups and physical, chemical, and microbial contamination. Packaging materials must also be protected against deterioration. Establishments that do not now perform these requirements and the other provisions associated with holding will incur a compliance cost.

iv. *Consumer complaints.* The quality control unit must review all consumer complaints involving the failure of a dietary supplement to meet any of its specifications, or the failure to meet any other requirements under proposed part 111, including those specifications and other requirements that, if not met, may result in possible illness or injury. In addition, the quality control unit must investigate such a consumer complaint where there is a reasonable possibility of a relationship between the consumption of a dietary supplement and an adverse event. The complaint and report of the investigation results should be reported to FDA when there is a possibility of a serious adverse event.

c. *Major costs by type of activity.* Within these four categories (sanitation, production and process controls, holding and distributing, consumer complaints), the major costs of the proposed rule are recordkeeping (except for sanitation), capital costs for physical plant and equipment, finished product quality testing (part of production and process controls only), labor costs for certain required tasks, and some other costs that were not easily classified.

i. *Recordkeeping.* We used a study of a medical device CGMP regulation to estimate the costs of recordkeeping (Ref. E44). We request comments on the applicability of a study of the medical device CGMP's to dietary supplements.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use mandatory records is a recurring cost that depends on how frequently records are modified, the frequency of personnel turnover, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate, which we assumed is $15.65 per hour based on the average manufacturing wage, multiplied by the expected labor hours necessary to perform a written or electronic record and the time necessary for management to review the records to see the actions are documented accurately. For electronic records, the recurring time is the time necessary to ensure that the equipment is serviced and maintained properly.

ii. *Capital costs for physical plant and equipment.* We estimated capital costs for physical plant redesign at $50 per square foot (Ref. E45). For establishments with inadequate facilities, we assumed that between 0 and 20 percent of the physical plant would have to be renovated, with 10 percent the most likely. For equipment costs, we assumed that very small establishments would on average spend 0 to $1,000, with $100 the most likely amount. Small establishments would bear costs 3 times that of very small establishments, which is the ratio of the size of the physical plants of small establishments to the size of the physical plants of very small establishments. We assumed that large establishments would bear (if necessary) costs 20 times that of very small establishments, which is the ratio of the size of the physical plants of large establishments to the size of the physical plants of very small establishments. In other words, we assumed capital costs for physical plant and equipment would be proportional to facility size, as measured in square feet.

iii. *Testing.* Establishments that do not already conduct the required product quality tests of each batch of dietary ingredients or dietary supplement produced would incur the cost for those tests. Under the option for more restrictive CGMP rules, each lot of components would also be tested. The costs per establishment depend on both the number of tests and the costs per test. We did not estimate the cost of developing new, validated tests methods because we lacked information about the costs for this requirement and the number of such tests that need to be developed. We ask for comments on the costs to develop tests, for the number of tests and the costs for performing each test to comply with this requirement.

- Number of tests: Model. To estimate the costs of testing, we first estimated the number and costs of individual tests, without adjusting for the amount of testing already being done. In this section we show how we estimated the likely number of required tests, unadjusted for current voluntary testing. For a representative manufacturer, the annual number of tests would be the number of new tests per batch multiplied by the number of batches produced in a year.

The proposed rule requires only tests for identity, purity, quality, strength, and composition of the final product. The option for stricter CGMP regulations would also require tests of components. Estimating the number of component tests per batch is complicated, because component tests are made on the shipment lots, rather than on the parts of the lots that actually go into the final product. For example, if a lot of some ingredient is used in 6 batches of final products, it would probably be tested only once.

The establishment itself may test the shipment lots, and during inprocess stages for identity, purity, quality, strength, and composition, unless final product testing is done.

The number of component tests per batch of final product would equal the number of tests per component, multiplied by the number of components per batch, divided by the batches per shipment lot (to account for the production of multiple batches of dietary supplements from single lots of components).

The option for stricter CGMP regulations options would also require some inprocess tests upon receipt. The number of inprocess tests per batch is the same as the number of potential inprocess product defects. The estimated number of inprocess tests counts only tests for defects that can occur during production, not tests for the defects of dietary ingredients and components supplied to the producer.

We used the following formulas to estimate the number of tests:

$$\text{Component test per batch} = \left[\sum m_j\left(I_j \times R_j\right) + \sum {}_k^n\left(U_k \times R_k\right)\right] \times (S/B)$$

$$\text{Inprocess quality tests per batch} = \sum {}_1^o\left(H_1 \times R_1\right)$$

Quality tests per batch of final product = max [m × (1/z), 1]

Where:

$I_j$ = jth listed ingredient;

m = number of ingredients per batch;

$R_j$ = required tests for ingredient j;

$U_k$ = kth unlisted component (an inactive substance);
n = number of unlisted components per batch;
$R_k$ = required tests for unlisted component k;
S = number of shipments (or lots) of ingredients and unlisted components;
B = number of batches produced;
$H_1$ = 1th inprocess potential defects;
$R_1$ = required inprocess tests per batch for potential defect $H_1$;
o = number of potential inprocess defects per batch;
z = number of ingredients identified per quality test.

• Number of tests: Evidence and distributions. The quantity and quality of evidence on the variables used to estimate the number of required tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

• Number of ingredients. We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E46). Although some dietary ingredients may be missing from the labels and some listed dietary ingredients may be missing from the products, the ingredient list represents the best evidence we are likely to have on what dietary ingredients are used in dietary supplements.

• Number of ingredients per batch. According to the sample of listed ingredients (Ref. E46). Vitamin and mineral products contain about 13 listed ingredients. Other dietary supplements, mainly herbals, contain about four.

• Number of tests per ingredient lot. The option for more restrictive CGMP regulations would require that virtually all dietary ingredients be tested for identity and defects at some stage between harvesting the raw product and the beginning of the production of the final product. We assumed one identity test per ingredient lot. The number of tests for defects depends on the number of possible defects, which can include: Filth; Microbial pathogens; Chemical hazards, including pesticides; Insects; Physical hazards, such as metals; Natural toxins, such as aflatoxin; and Inadequate purity, quality, strength, or composition.

The number of potential defects is potentially unlimited. As a practical maximum, however, few products would have more than five potential defects. In the calculation of ingredient testing costs (part of the option for more restrictive CGMP regulations), we assumed that the average number of tests per listed dietary ingredient would be between one and six: One identity test for identity, purity, strength, quality, and composition and zero to five tests for defects.

• Number of unlisted components. Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E47) says that four to six unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. We assumed that the number of unlisted components would be zero to six, with four the most likely.

• Number of tests per unlisted components. The unlisted components tend to be manufactured products, such as solvents. Therefore, one identity test would likely be sufficient.

• Number of shipments (or lots) of ingredients and unlisted components. We have no direct evidence on the number of shipment lots of dietary ingredients and components. We also have no evidence on the number of shipments per lot or on the number of shipments per batch. The increasing use of just-in-time inventory practices indicates that one shipment lot of components per batch may be the rule for some products and some producers. It is costly and difficult to store ingredients for an extended time, so establishments tend to buy more and smaller lots of components rather than a few large lots and storing them in bulk over an extended period (Ref. E48). Crude botanical and other ingredients are inherently unstable and may lose their quality in even a short time unless costly temperature, humidity, and light controls are in place (Ref. E49). We also know, however, that some dietary ingredient suppliers produce large amounts and then ship out smaller packages. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per lot could be large. Also, some producers buy a single shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. In the cost calculation, we assumed that 1 was minimum and 12 the maximum number of batches produced per lot, with 6.5 the average.

• Number of batches produced. We have survey results (Ref. E2) on the number of batches produced per establishment. According to the survey, very small establishments produce an average of 223 batches per year, small establishments produce an average of 554 batches per year, and large establishments produce an average of 309 batches per year.

• Inprocess potential defects. Inprocess defects involve many of the same potential defects that can occur in components. The more restrictive CGMP option requires inprocess tests at all points where contamination or other defects can occur. Filth, chemicals, microbial pathogens, physical objects, and insects can be introduced into the product during manufacturing. In addition, purity, quality, strength, and composition can be compromised.

• Number of potential inprocess defects. Some processes may have no control points, steps, or stages that involve the potential for defects. If certain manufacturing processes in the production of a dietary supplement can be carried out without being subject to potential defects, no inprocess tests would be required for those processes. We therefore assumed that zero inprocess tests would be the lower bound requirement. For the upper bound, we assumed that no products would have more than five potential control points or steps that could lead to defects. We believe that most production processes will have fewer than 5 control points, so we assumed an average of 2.5 control points requiring inprocess tests for defects.

• Number of required inprocess tests per control point. We assumed one test per defect per control point.

• Number of ingredients identified per quality test. We had no direct evidence on the number of identity tests per final dietary supplement. For the maximum, we assumed that the number of tests would equal the number of ingredients. The number of ingredients identified per test varies from less than one to a very large number. We assumed that for vitamins and minerals, the minimum number of identity tests would be one and the maximum would be 30, with 2 the most likely. Botanical and herbals are less easily characterized than vitamins; so identifying large numbers of ingredients with a single test would be highly unlikely. We assumed that one to two ingredients would be identified per test for herbal products.

• Number of final product tests per batch. We had no direct evidence on the number of quality tests per final dietary supplement. After adjusting for the possibility of multiple results from a single test, multiple ingredients in single products, and the differing number of ingredients in herbal and vitamin products, we estimated that the proposed rule would require about three tests for identity, purity, quality, strength, and composition for each batch of final product. These are the

only required tests in the proposed rule, but establishments may choose to perform inprocess tests and tests on ingredients in order to prevent waiting until final product testing to discover defects.

iv. *Costs per test.* We estimated the costs per test partly with published prices of independent laboratories as posted on the Internet (Refs. E50 and E51), and partly from our conversations with FDA and industry experts on testing. We found that testing costs vary according to frequency and complexity. The more frequently technicians perform tests, the lower are the costs per test. Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment. Using sophisticated equipment requires trained personnel. Even simple physical or organoleptic testing requires training or experienced personnel. The type of ingredient, compound, or product can also affect the cost because some are easily identified using routine or single step techniques and others require multiple steps or complex techniques, especially if there are similar products that can be mistaken for the products being identified. The type of defect tested for affects the cost; some defects can be found visually if they are found on the surface, but others are latent. Some tests require multiple samples or multiple steps. In addition, tests require the taking and of samples, whose cost can vary.

We assumed that $20 per test represented a plausible lower bound. This cost represents the full cost of carrying out a test, including collecting and storing the sample, the time for training the personnel who carry out the test, and any associated records. Although some Internet testing prices for tests were as high as $300, we assumed that with frequent testing $150 would be a more plausible upper bound average cost. The majority of listed prices fell into the $20 to $80 range, so we selected $50 (the midpoint) as most likely. The average cost per test was about $60.[8]

Changing our assumption about the midpoint of testing costs would change our estimate of the cost of the rule. If the cost of testing each batch is actually significantly higher, then the impact to those firms that incur the cost and to society will have been understated.

v. *The number and cost of tests: summary.* We estimated the number of tests required of the representative manufacturer as a weighted average of the number of tests required for vitamins and minerals and the number of tests required for all other supplements (which were mainly herbal products). We used survey responses to a question about the establishment's primary line of business for the weights used to compute the average number of tests. We dealt with multiple responses by treating all nonvitamin and nonmineral responses as other dietary supplements. The following weights, as shown below, differed by size of manufacturer:

- 24 percent of very small manufacturers produce vitamins and minerals; 76 percent produce other dietary supplements.
- 42 percent of small manufacturers produce vitamins and minerals; 58 percent produce other dietary supplements.
- 69 percent of large manufacturers produce vitamins and minerals; 31 percent produce other dietary supplements.

The annual cost of testing differed by the size of the firm, because the average number of batches produced differed. For the option calling for more strict regulation, the total costs of testing would be much higher than in the proposed rule. The unadjusted total cost of testing under the more restrictive CGMP option would be:

$148,000 for very small establishments;
$415,000 for small establishments;
$263,000 for large establishments.

We estimate that the adjusted total cost for testing for the proposed regulation will be:

$11,230 for very small establishments;

$19,907 for small establishments;

$7,626 for large establishments.

We found some corroboration for these estimates in a comment on the Advance Notice of Proposed Rulemaking entitled ''Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements'' published in the **Federal Register** of February 6, 1997 (62 FR 5699 to 5709). According to the comment, the cost of testing components and final products inhouse would be at least $650 per batch plus microbiological tests. Testing costs could be more if establishments sent samples to independent laboratories for testing or if they conducted extensive identity tests of herbal and botanical products. If we apply the $650 to the annual number of batches per establishment, the comment implies that very small establishments would perform $145,000 ($223 \times \$650$) worth of tests, small establishments would perform $360,000 ($554 \times \$650$) worth of tests, and large establishments would perform $200,000 ($309 \times \$650$) worth of tests. These estimates are reasonably close to our simulation estimate.

The unadjusted testing costs represent the total requirements and recommendations, not the additional costs that would be incurred in response to the proposed rule. Tests on incoming components and inprocess tests would not be required by the proposed rule. Most establishments already conduct some tests, or send samples out for testing. We, therefore, adjusted the estimated testing costs of the proposed rule to include only required tests and to account for the testing costs currently borne voluntarily by manufacturers. The survey results showed how many respondents were conducting various types of tests.

TABLE 14.—VALUES USED IN TESTING COST CALCULATIONS

| Name | Value or distribution used | Source |
|---|---|---|
| Number of dietary ingredients per product batch | Vitamins and minerals—13; All other categories—4. | Sample from 3,000 dietary supplement labels (Ref. E46). |

[8] The average cost is higher than the most likely cost because we modeled costs with a Beta-Pert distribution that was skewed rightward (toward higher costs). The Beta distribution is part of the Bernoulli family of distributions and is closely related to the Binomial. The Binomial gives the distribution of the number of successes (s) in n trials if the probability of the success in each trial is p. The Beta shows the distribution of the value of p when s successes occur in n trials. The Beta-Pert distribution is a Beta distribution that has been rescaled to run between values other than 0 and 1. The Beta-Pert uses a minimum, maximum, and most likely value to generate a distribution running from the minimum to the maximum, with a mean equal to (minimum + (4 × most likely) + maximum)/6. We used the Beta-Pert distribution because we did not have a representative sample to derive the distribution, but we did have enough information to identify a plausible maximum, minimum, and most likely value. The use of the Beta-Pert, then, indicates that we do not know the shape of the probability distribution of possible testing costs, but we do have limited data.

TABLE 14.—VALUES USED IN TESTING COST CALCULATIONS—Continued

| Name | Value or distribution used | Source |
|---|---|---|
| Number of identify tests per ingredient lot | 1 Identity test per ingredient lot | Assumption based on discussions with industry—FDA requests comments. |
| Number of tests for defects per ingredient lot | 0 to 5 tests for defects | Assumption based on discussions with industry—FDA request comments. |
| Number of unlisted components | 0 to 6 components; 4 most likely | Ref. E47. |
| Number of tests per unlisted components | 1 identity test per component | Assumption based on discusssions with industry—FDA requests comments. |
| Number of shipments (Lots) of ingredients and unlisted components. | 1 to 12 batches per shipment lot of dietary ingredients. | Assumption based on discussions with industry—FDA requests comments (Ref. E48). |
| Number of batches produced | Very small establishments—223; Small establishments—554; Large—309. | Ref. E2. |
| Number of inprocess potential defects | 0 to 5 potential control points; 2.5 average | Assumption based on discussions with industry—FDA requests comments. |
| Number of inprocess tests per control point | 1 test per defect per control point | Assumption based on discussions with industry—FDA requests comments. |
| Number of ingredients identified per identity test | Vitamins and minerals—1 to 30; 2 most likely; All other categories—1 to 2. | Assumption based on discussions with industry—FDA requests comments. |
| Number of final product tests per batch | 3 tests batch | Assumption based on discussions with industry—FDA requests comments. |
| Costs per test | Beta per distribution skewed rightward between $20 to $150; $50 most likely; $60 average. | Refs. E50 and E51. |

vi. *Labor costs.* We used the average manufacturing wage of $15.65 per hour to estimate the cost of labor. We assumed that various tasks required by the proposed rule would take some number of hours per year, per batch of product, or per square foot of physical plant. For example, we assumed that time spent on the sanitation of physical plants is a function of the square footage. We assumed 1 hour per week for very small establishments, 3 hours per week for small establishments, and 20 hours per week for large establishments. We request comment or data about costs, hours, and the other requirements for these proposed required procedures.

vii. *Other costs.* The main costs in this category are for pest and rodent control. We consulted a commercial supplier of these services for the estimated monthly costs, which were $400 to $600 a month for very small establishments, $480 to $720 for small establishments, and $700 to $1,000 for large establishments (Ref. E52). For each size of establishment, we selected the midpoint of the range as the most likely value.

d. *Estimating costs.* We initially gathered information and made assumptions about the full cost of a provision. We then adjusted these estimates to account for the many activities already being carried out, as well other activities that would not have to be carried out by all establishments. We used the survey to estimate the likelihood that an establishment would incur a cost. To get an estimate of the average cost of provision (adjusted for baseline activities) for each category, we multiplied the average cost per establishment by the probability that the establishment would need to undertake the expense (one minus the probability that the establishment was already doing it). For each provision of the proposed rule, the simulation carried out the following calculation:

Cost per unit of analysis for each provision = number of units of analysis per establishment × probability that establishment incurs cost × adjustment for requirement (yes or no) = cost per provision per establishment

We estimated both a setup cost (a one-time fixed cost) of the provision and an annual recurring cost. The first-year costs would be the setup costs plus the annual costs. To get the total costs of the rule, we multiplied the number of establishments in each size category (from the survey) by the average costs per establishment in that category. We then adjusted for the establishments that did not respond to the survey but are believed to be in the industry. Two hundred thirty eight establishments responded to the survey; we estimated that 1,566 firms are in the industry. We estimated costs with the following calculation:

[Number of very small establishments × costs per very small establishment) + (Number of small establishments × costs per small establishment) + (number of large establishments × costs per large establishment)] × adjustment for establishments not in survey

The rule is complex and the industry is made up of very different kinds of firms, so cost estimates are averages with, in some cases, large variances. The cost per unit, number of batches and employees, and probability that the establishment would incur the cost all contain uncertainty. The values in table 15 of this document are used in the cost estimates, and are generated from multiple sources.

TABLE 15.—VALUES USED IN COST CALCULATIONS

| Name | Value or distribution used | Source |
|---|---|---|
| Average wage per hour | $15.65 | Employment Index, Bureau of Labor Statistics. |
| Average size of establishments in square feet | Very small = 24,674; small = 71,354; large = 596,000. | Ref. E2. |
| Average number of employees | Very small = 7.6; small = 95; large = 1,005 | Ref. E2. |
| Average annual number of batches | Very small = 223; small = 554; large = 309 | Ref. E44. |

TABLE 15.—VALUES USED IN COST CALCULATIONS—Continued

| Name | Value or distribution used | Source |
|---|---|---|
| Annual time recordkeeping | 1/10 of setup time per provision | Ref. E44. |
| Personnel sanitation | 1 hour per week per worker | Assumption, based on requirements of proposed rule. |
| Sanitation time for physical plant | 1 hour per week for very small establishments; 3 hours per week for small establishments; 20 hours for physical plant per week for large establishments. | Assumption, based on difference in average physical plant size. |
| Sanitation supervisor | Very small and small establishments = 1 hour per week; large establishments = 1 hour per week. | Assumption, based on number of workers. |
| Pest control setup costs | $1,500 to $2,000 for very small establishments; $1,800 to $2,400 for small establishments; $2,600 to $3,400 for large establishments. Average for each size establishment was midpoint ($1,750, $2,100, $3,000). | Ref. E52. |
| Pest control annual costs | $400 to $600 per month for very small establishments; $480 to $720 for small establishments; $700 to $1,000 for large establishments. Average for each size establishment was the midpoint ($500, $600, $850). | Ref. E52. |
| Renovation cost | $50 per square foot; with 0 to 20 percent of physical plant to be renovated, with 10 percent most likely. | Based on construction costs and square feet. |
| Minimum quality control unit | 1 person or 1 percent of establishment work force. | Assumption based on requirements of proposed rule. |
| Equipment replacement | For very small establishments, 0 to $1,000, with $100 most likely; small, 0 to $10,000, with $1,000 most likely; large, 0 to $100,000 with $1,000 most likely. | Assumption, based on size of establishments. |
| Setup costs for automatic equipment | $500 for hardware, 16 hours | Software costs and assumptions about labor hours. |
| Annual costs for automatic equipment | 1 to 2 hours per month for very small and small establishments; 2 to 4 hours per month for large establishments. | Assumption based on average size of establishments. |
| Sanitation of equipment and surfaces | 5 hours per week for very small establishments, 15 hours per week for small establishments, 100 hours per week for large establishments. | Assumption based on average sizes of establishments. |
| Number of dietary ingredients per batch, supplements other than vitamins. | 12.8; standard deviation = 15.6 | Ref. E46. |
| Number of dietary ingredients per batch, supplements other than vitamins. | 3.6; standard deviation = 4.8 | Ref. E46. |
| Cost per test | $20 to $150, with $50 most likely | See text discussion. |
| Holding products and dietary ingredients: capital requirements. | Setup cost for very small 0 to $1,000, with $100 most likely. Multiply by 3 for small establishments and by 20 for large establishments. | Based on average sizes of establishments. |
| Default probabilities that establishments are not currently acting in accordance with a provision. | For very small establishments, 0.2; for small establishments, 0.1, for large establishments, 0.01. | Based on results of survey for other practices. |

We combined the costs per establishment with the number of establishments and probabilities from the survey, and adjusted for establishments not in the survey to estimate the total costs of the proposed rule. Table 16 of this document summarizes the estimated total costs for very small establishments, small establishments, large establishments, and warehouses. Table 17 of this document shows the total costs for the first year and annually after the first year, assuming that the proposed rule is phased in over 3 years. Table 18 of this document shows the total costs of the proposed rule compared to the total costs of other options.

TABLE 16.—SUMMARY OF COSTS BY SIZE OF ESTABLISHMENT

| | Number of establishments | 1st Year costs per establishments | Annual costs per establishments | Total 1st year costs (in millions) | Total annual costs (in millions) |
|---|---|---|---|---|---|
| Very small establishments | 740 | $62,000 | $38,000 | $46 | $28 |
| Small establishments | 766 | 99,000 | 61,000 | 76 | 47 |
| Large establishments | 60 | 83,000 | 47,000 | 5 | 3 |
| Warehouses and other holders | 26,617 | 436 | 342 | 12 | 9 |

TABLE 17.—ESTIMATED TOTAL COSTS

[In millions]

| | 1st Year | 2nd Year | 3rd Year | 4th Year and after |
|---|---|---|---|---|
| Very small establishments | 0 | 0 | $46 | $28 |
| Small establishments | 0 | $76 | 47 | 47 |
| Large establishments | 5 | 3 | 3 | 3 |
| Warehouses | 12 | 9 | 9 | 9 |
| Total | 17 | 88 | 105 | 87 |

8. Summary of Benefits and Costs

We estimated that, once it is fully implemented, the measured annual benefits from the proposed rule would be $218 million; measured annual costs would be about $86 million. Additional but unmeasured benefits should also be recognized when comparing the total costs and benefits. Table 18 of this document compares the benefits and costs of the proposed rule to the benefits and costs of the leading regulatory options. Because the phase in period, complicates the comparison for the early years, we limit the comparison to annual benefits once all establishments are covered.

TABLE 18.—ANNUAL BENFITS AND COSTS OF REGULATORY OPTIONS

[In millions]

| Regulatory option | Annual benefits | Annual costs |
|---|---|---|
| Proposed rule | $218 | $86 |
| Fewer requirements for vitamins and minerals | 109 | 69 |
| Stricter CGMP | 218 | 178 |
| HACCP only | 42 | 38 |
| Testing only (unable to estimate) | | 32 |
| High risk products only (unable to estimate) | | (1) |

[1] Less than $86 million.

*Uncertainties in the analysis.* In this section, we list all of the significant assumptions in the analysis, which if varied, could significantly change the estimates of costs and benefits. Such changes could have importance for the construction of any potential final rule. Therefore, we ask that comments address these aspects of the analysis and, where possible, provide FDA with better data to reduce the uncertainty. We estimated the benefits using indirect methods, which required several key assumptions that are critical for our estimates. With the exception of the recall benefit, which is based directly on FDA recall records, each component of the estimated benefits involves assumptions that reflect our uncertainty.

Our basic assumption is that manufacturers lack market-based incentives to prevent hidden product quality defects. Our survey (Ref. E2) indicated that many firms do not have reliable quality control mechanisms in place. The survey was a one-time look at the manufacturing practices during the time of the survey. If the trend in the market is toward the adoption of the controls that we are proposing here in the absence of regulation, then both the cost and benefits of the rule will be less than we estimate. If the market-based trend is toward fewer controls, then both the cost and benefits of the regulation will be greater. Other key assumptions are listed below:

The assumptions for the health benefits from reducing the number of sporadic illnesses model are:

1. The baseline health of consumers is normal, not perfect. To estimate the change in health status from consuming defective products, we assumed that the baseline health of consumers is normal, which does not mean that we assumed that consumers have perfect health. We recognize that consumers will already have ''background'' health problems, by which we mean that many will have health problems unrelated to the consumption of defective products. Our assumption is that only the change in health status is relevant for our analysis. If an immune-compromised consumer is made ill by a defective product, *e.g.*, gets lead poisoning, the consumer might in fact have more difficulty recovering than an otherwise healthy person. However, we assume that the change in productivity, functional state, pain and suffering, and medical costs will be the same, regardless of prior health status. Accounting for confounding factors would have the effect of making health problems worse than we estimate, not better, so our estimate may be understating the true health benefits.

2. The average value of a QALY is $630 per day. That value, $630 per day, is in turn based on: (1) The value of a statistical life of $5 million; (2) the expected remaining life of consumers of 21.84 years (average), discounted from 36 years; and, (3) the social rate of time preference of 3 percent. The estimate is derived from workers in somewhat risky occupations who demand a wage premium for their additional risk of fatality. If our estimate of the value of a statistical life of workers does not represent the value of a statistical life of consumers of dietary supplements, then our benefits estimate will be different from the true health benefits of the rule. If consumers value their life differently than workers or if consumers place different values for different kinds of hazard-related deaths than do workers for job-related safety hazards, then we will have incorrect estimates for the true health benefits. If we discount life expectancy by 7 percent instead of 3 percent, the benefits would be much higher.

3. There is one illness for each recall. We assumed that for each class 1 and 2 recalled product there was only one illness that was reported to the public health authority. For instance, if a product was recalled because the defective product contained lead, we assume that a person was made ill from lead poisoning and that was how the recalled product was discovered. If there were more illnesses per recall than one, then our estimates of benefits will be low. If fewer than one illness per recall occurred (or is likely to occur in the future), then our estimate of health benefits will be more than the actual health benefits.

4. The assumed frequency of actual illnesses is 100 times the frequency of reported illnesses. This assumption is based on Ref. E16. We recognize that the factor of 100, although it has empirical support, might be wrong and that there is likely to be considerable uncertainty about this point estimate. It is widely believed in the public health community that most illnesses are underreported to public health authorities, particularly in passive reporting systems, such as the case with

dietary supplements. Mild cases are the most underreported. For instance, victims rarely notify public health authorities when they have minor gastrointestinal tract related illnesses. It is even more rare to report the likely source of a mild illness. It is also widely believed that severe illnesses and death are reported much more frequently than milder illnesses, even when the cause of illness or death is not included in the report. Although the number of deaths that are reported probably approach 100 percent, the cause of death from a contaminated dietary supplement product might not be reported. We believe that using a single composite factor—100—to represent the total number of all unreported cases, including mild, severe, and death, does not invalidate our assumption. The factor of 100 represents an estimate of the composite probability of the full range of probabilities for each severity level of an illness being reported. Increasing the factor multiplier from 100 to some number higher would increase the health benefits, while lowering the multiplier would decrease the health benefits. If we assume that all illnesses are reported—there are no unreported illnesses and no factor of 100, then the health benefits from fewer sporadic illnesses will be less than $1 million.

5. Introducing CGMP's will reduce the probability of a recall to zero. We believe that the proposed CGMP's creates the most reliable means for discovering product adulteration. Indeed, we believe that it will, if strictly used, cause the discovery of all adulteration. Therefore, we assume that once an establishment fully adopts the requirements, there should be no more health risk from adulterated dietary supplements and consequently, no more class 1 and 2 recalls. This conclusion rests on the assumption that there will be 100 percent compliance with this regulation. We recognize that human error is inescapable. If recalls—or a health risk from adulteration—would still exist, then we overstated the true health benefits of the regulation.

The assumptions for the health benefits from lowering the likelihood of rare catastrophic event model are:

1. We assume that a rare catastrophic event would occur every 30 years. We recognize that the occurrence of a single event provides little evidence about what will happen in the future. If the event reported in this analysis was in fact a one-time occurrence, then our estimate of the benefits from the prevention of the catastrophic health event would overstate the true benefits, which in fact should be zero. There would have been no future event, and there would be no benefit from adopting a rule to avoid it. If a rare event would have happened more frequently than our estimate of once every 30 years, then our estimate of the benefits would underestimate the true health benefits.

2. Number of illnesses per rare event. We based our estimate of the health impact from contaminated L-Tryptophan. If the number of illnesses from a future rare event differed—either more or less—then the health benefits would differ from our estimated benefits. If a future event would have had 10,000 cases, not 1,500 cases, then our estimate would understate the true health benefits of avoiding such a large catastrophe.

The assumptions for fewer products recalled are:

1. The reported class 1 and 2 recalls that have occurred over the last 10 years represent the number and type of recalls that would have occurred in the future but for the implementation of this regulation. If the number or types of recalls are not representative, then we over or under estimated the benefit of avoiding recalls. Avoiding one very large recall could result in significantly higher benefits. Conversely, merely avoiding fewer or smaller recalls would result in smaller benefits.

2. A product recall causes sellers to lose both goodwill and the value of the recalled product and lost goodwill equals the value of the recalled product. These two embedded assumptions have empirical support from Ref. E24. A product recall adversely affects the wealth of sellers—a recall leads to lost goodwill—by signaling to consumers that products are defective. From evaluating the declines in public share prices after product recalls in various industries, the authors in Ref. E24 determined that the loss in share price is twice the value of the loss of the actual value of the product recalled. They attribute the difference to lost firm goodwill.

3. Full compliance with the proposed CGMP's will reduce the probability of a recall to zero. As in our earlier assumption about the probability of recalls after the rule is adopted, consistency requires that if we believe that the rule will reliably cause the discovery of adulterated products before they are commercially available, there should be no more health risk from adulterated dietary supplements. Consequently, there should be no more recalls.

We developed the hypothetical search model to estimate the implicit value to consumers of better product quality although we lacked a model that could enable us to directly estimate consumer preferences for dietary supplement quality. With the adoption of the proposed rule, the standardization of manufacturing practices will reduce product differentiation. In a perfect information market, the change in product differentiation would be reflected in the change in the price differences between low and high quality products. In the existing market, price differences alone are an inadequate signal because the differences in product quality are typically hidden from the view of both consumers and (though less so) manufacturers. In this hypothetical model, we assumed that if there were actually indicators of product quality in the market now, consumers would spend a certain amount of time attempting to find a reasonably high quality product. Time spent searching is an economic cost. In fact, in markets where quality is discernible prior to purchase, such search does take place and it is from those markets that our estimates were derived. In such a world of easily available product quality signals, this regulation, by standardizing product quality at the high end, would reduce that search time. Our assumption is that this is a reasonable indicator of consumers' value for high quality products. Further, we assume that in fact consumers of dietary supplements do wish to purchase high quality products, as the absence of quality could mean either an ineffective product or worse, illness or death. We used various assumptions at each step in our model, and the benefits change when the assumptions change. The assumptions that we used for the search model are:

1. Consumers will search until the expected benefits of the search equal the expected cost of additional search. The expected cost is the value of their time, which we estimated is the average wage rate for manufacturing workers—$15.65/hour. If the true wage rate is different, the benefits of the rule will be different.

2. The three models—drug store, use of time and grocery store models—represent consumers of dietary supplements. If not, then we will not have estimated the true preferences of consumers. If consumers value dietary supplements more highly than either drugs, groceries or other uses of time, and they search more for better quality, then we understated the benefits of product standardization. If consumers value dietary supplements less highly than either drugs, they search more for better quality, then we overstated the benefits.

3. The quality controls will reduce consumer search time by approximately

33 percent. If our estimate is not representative of the true average reduction, then our estimate will be wrong.

4. The type and number of consumers represent the true value. If children, the elderly or other consumers search for these products in significantly greater amounts than average workers or the estimated population, then we may have overstated the benefits, because their foregone wages would be less than that of average workers.

In an ideal analysis, the benefits and costs of each provision would be evaluated. We were not able to quantify the benefits for each of the provisions in our analysis although we do have fairly detailed estimates of the cost. We request comments on marginal costs and benefits of specific provisions in the rule. Comments can be directed either at how well a specific provision might work to make dietary supplements either safer or of higher quality, or be directed at the cost of the provision. An example of this type of provision follows for recordkeeping:

Benefits of Recordkeeping

Mandatory recordkeeping is intended to help the discovery of manufacturing practices that create defective products. Recordkeeping ensures that preventative controls are carried out for each batch of dietary supplements produced. Records serve as a checklist that quality control personnel can consult to monitor that necessary controls are implemented or corrective actions taken. Further, mandatory recordkeeping provides an incentive for manufacturers to comply more fully with the provisions of the rule where recordkeeping is required. Knowing that FDA inspectors will examine records and that falsifying them is a criminal offense provides strong incentives to keep thorough and accurate records that the required safety functions have been performed adequately and in a timely manner. Thus, the benefits of recordkeeping are to permit detection of defective products and increase compliance with the provisions for which recordkeeping is required. If, for example: (1) The total benefits of the requirements that have recordkeeping attached to them were $50 million (not the real value); (2) only half of the requirements would be met without recordkeeping; and, (3) recordkeeping raised the compliance rate to 100 percent, then the benefits of recordkeeping would be $25 million. We were not able to quantify the marginal benefits of this requirement with numbers like this. Comments are requested for how well records are likely to perform this function. We estimate that the additional cost to society for the proposed new recordkeeping requirement will be approximately 10 percent of the total annual cost of the proposed regulation, or a little less than $9 million per year.

Further, we request comments on all of the provisions that would be of a similar nature to this example.

The costs of the rule depend on our assumptions about the amount and cost of testing. The amount of testing is highly uncertain; we have tried to model the number of tests based on number of ingredients and types of tests.

We first characterized the uncertainty as a probability distribution. We ran 1,000 computer simulations to estimate both benefits and costs. The simulations used distributions and assumptions from tables 8 through 13 of this document in place of single estimates.

TABLE 19.—DISTRIBUTION OF SIMULATION RESULTS FOR ANNUAL BENEFITS AND COSTS

[In millions]

| | 5th Percentile | Median | Mean | 95th Percentile |
|---|---|---|---|---|
| Annual benefits | $89 | $198 | $218 | $405 |
| Annual costs | 62 | 80 | 86 | 128 |

The computer simulation gives the distribution of estimated benefits and costs. If the underlying distributions capture the uncertainty of the estimates, then the results in table 19 of this document give a clear picture of the uncertainty. Another way to show the uncertainty is to see how sensitive the results are to plausible changes in individual variables. We start with benefits.

TABLE 20.—SENSITIVITY OF BENEFITS

[In millions]

| Description | Estimated annual benefits |
|---|---|
| The proposed rule | $218 |
| If reporting rate of illness is 0.1 (baseline is 0.01) | 182 |
| If reporting rate of illness is 0.005 (baseline is 0.01) | 257 |
| If the value of a statistical life is $3 million (baseline is $5 million) | 175 |
| If the value of a statistical life is $7 million (baseline is $5 million) | 259 |
| If consumer search time per item is 1 minute (baseline is 3.75 minutes) | 137 |
| If consumer search time per item is 5 minutes (baseline is 3.75 minutes) | 250 |
| If consumer search time equals 40 percent of shopping time (baseline is 70 percent) | 166 |
| If consumer search time is equal to shopping time (baseline is 70 percent) | 254 |
| If consumer search for quality accounts for 30 percent of search time (baseline is 20 percent) | 278 |
| If consumer search time for quality accounts for 10 percent of search time (baseline is 20 percent) | 158 |
| If catastrophic events are not prevented (baseline is $66 million annual benefit from prevention) | 152 |

We mainly looked at the cost effects of changing assumptions about testing and consumer complaints. As table 21 of this document shows, annual costs are quite sensitive to the assumptions about the average cost and number of tests.

TABLE 21.—SENSITIVITY OF COSTS

[In millions]

| Description | Estimated Annual Costs |
|---|---|
| The proposed rule | $86 |
| 6 tests per batch (baseline is 3) | 119 |
| 1 test per batch (baseline is 3) | 66 |
| $100 per test (baseline is $60) | 101 |
| 1 consumer complaint per 20 batches (baseline is 1 per 10) | 77 |
| 1 consumer complaint per 5 batches (baseline is 1 per 10) | 104 |

*C. Initial Regulatory Flexibility Analysis*

1. Introduction

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. We find that this proposed rule would have a significant economic impact on a substantial number of small entities.

2. Economic Effects on Small Entities

a. *Number of small entities affected.* The proposed regulations would affect many small entities. Our classification of establishment size is based on the Small Business Administration's definition for small, as discussed previously in this document. A small business by this definition is any establishment with fewer than 500 employees. For this analysis, we defined very small establishments as establishments with fewer than 20 employees. Some small and very small establishments produce very large revenues and would probably not incur a large decline in profitability from the proposed CGMP regulations. We lack precise information about those establishments. Based on the survey, we estimated that 830 establishments, 53 percent of the total establishments, could be classified as very small (under 20 employees) and 564 as small (20 to 499 employees), which is 36 percent of the total establishments.

We estimated that 95 percent of all holders (warehouses and wholesalers) covered by this regulation are small using the Small Business Administration definition. The total number of holders likely to be affected by this regulation is 26,617 (*see* table 4 of this document), so the total number of holders that are small would be 25,286 (= $0.95 \times 26{,}617$).

The small establishments that would be affected by the proposed regulations are those establishments that would have to perform the various required activities, and that would not have done so without the regulations. As in the preliminary regulatory impact analysis (section VII.B of this document), we determined our estimate of baseline (pre-CGMP) manufacturing practices with the survey of the industry (Ref. E2). The survey asked representative respondents to answer a series of questions, including how many employees they had and what their existing practices were. From the survey, we determined that small establishments do not now follow all of the provisions of the proposed CGMP regulations now. Those that do not follow the proposed requirements will incur a cost to do so.

b. *Costs to small entities.* Implementation costs vary across establishments based on current practices and the types of products manufactured, packaged, or held. We estimated the range of current practices using the survey of the industry. The cost model divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 22 of this document shows the cost per establishment for very small and small establishments. For comparison, we include the estimated average cost per large establishment and the median revenues for each size category. As the table shows, costs per establishment are proportionally higher for very small than for large establishments. The table's most striking result is that costs are highest for small (20 to 499 employees) establishments.

TABLE 22.—COST PER ESTABLISHMENT

| | 1st year | Annual |
|---|---|---|
| Very small—fewer than 20 employees; median revenue under $1 million | $62,000 | $38,000 |
| Small—20 to 499 employees; median revenue $5 to 10 million | 99,000 | 61,000 |
| Large—500 or more employees; median revenue $20 to $50 million | 83,000 | 47,000 |

Small establishments that do not perform a substantial number of the actions required by the proposed CGMP regulations would bear relatively high costs for compliance with the provisions of this proposed rule. As shown in table 22 of this document, we estimated the average annual compliance costs for a very small establishment to be around $38,000. About one-third of those establishments or about 500 firms have annual sales revenues under $500,000. In addition, the average annual compliance cost for a small establishment is around $61,000. As the survey indicated, about 14 percent of establishments with 20 to 499 employees or about 200 firms have annual sales revenues under $500,000. For purposes of our analysis, we regard firms with revenues of $500,000 or less to be low revenue firms. Although the proposed rule would raise product prices, the price increase (which would largely be determined by changes made by large establishments) would be much smaller than the increase in the average costs of very small producers. The average burden to very small low revenue firms, then, would be at least 8 percent of their annual revenue. The average burden to small low revenue firms would be at least 12 percent of annual revenue. Establishments with above average costs, and even establishments with average costs,

would be hard pressed to continue to operate. Therefore, some of these establishments, for example, such as those that produce other products (foods or pharmaceuticals) or are part of firms with more than one establishment, may decide it is too costly and either change product lines or go out of business. If we assume that one half of these firms have sales revenues from other products and locations and remove them from the at-risk group, we are left with approximately 350 very small and small establishments with less than $500,000 in revenue. It is possible that a large number of these 350 very small and small establishments would be unable to absorb the compliance costs and will close.

3. Regulatory Options

a. *Exemptions for small entities.* The burden on small establishments would be reduced if they were exempt from some provisions of the proposed rule. Most entities affected by this proposed rule, however, are small. Exempting small establishments from some or all of its provisions would be likely to reduce benefits.

b. *Longer compliance periods.* Lengthening the compliance period would provide regulatory relief for small entities. A longer compliance period for small entities would allow additional time for setting up recordkeeping, making capital improvements to the physical plant, purchasing new or replacement equipment, and other one-time expenditures. It would also delay the impact of the annual costs of compliance. We have given very small and small firms an additional 2 years for compliance. The proposed rule, then, would be phased-in over 3 years, with large firms complying after 1 year, and both very small and small firms after 3 years. After 3 years, the annual costs would be incurred. The cost savings of delay may well be larger than simply the present value of the delay because very small and small firms may also be able to reduce their compliance costs by taking advantage of increases in industry knowledge and experience in implementing CGMP regulations. A summary of the compliance costs is shown in table 22 of this document.

Although lengthening the compliance period would provide some regulatory relief to small entities, relief for these provisions would also delay the full realization of the benefits of the proposed rule.

4. Description of Recordkeeping and Reporting

The Regulatory Flexibility Act requires a description of the recordkeeping and recording required for compliance with this proposed rule. This proposed rule would require the preparation of records. As described in the Preliminary Regulatory Impact Analysis, records must be written or electronic documents must be kept that demonstrate that specific action or actions occurred in the manufacturing process in compliance with the proposed regulations. Records that would be required in this proposed rule would demonstrate, that corrective actions were taken, that equipment, instruments, and controls used in laboratory operations and quality control were installed properly, and calibrated; that maintenance programs were followed; and that the results of any testing meet the necessary specifications.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use the new documents is a recurring cost depending on how frequently documents are modified, how often personnel turn over, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate multiplied by the expected labor hours necessary to perform a written or electronic record and the time necessary for management to review the records to see that actions are documented accurately. In addition, electronic records necessitate recurring time spent ensuring that the equipment is serviced and maintained properly.

5. Summary

The proposed CGMP regulations would have a significant economic impact on a substantial number of small entities.

*D. Unfunded Mandates*

The Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current inflation-adjusted statutory threshold is $112 million. The proposed rule qualifies as a significant rule under the statute because there is a significant possibility that the cost of the rule will be above the threshold. Most of the requirements of the Unfunded Mandates are fulfilled in the Executive Order 12866 analysis. The requirements under the Unfunded Mandates Act of 1995 include assessing the rule's effects on future costs; productivity; particular regions, communities, or industrial sectors; economic growth; full employment; job creation; and exports.

Future Costs

The future costs from the rule include the recurring costs, which reach their long-term value in the third year after the proposed rule would become final. These costs would be incurred by the establishments that manufacture, process, pack, transport, distribute, receive, hold, or import dietary ingredients or dietary products. Recurring costs from the regulatory requirements would be incurred in each future year. Table 18 of this document summarizes the annual future recurring costs.

Particular Regions, Communities, or Industrial Sectors

The costs of the rule will be shared among manufacturers, processors, packagers, transporters, receivers, holders, and importers of dietary ingredients or dietary products as well as domestic consumers. The higher costs incurred by domestic suppliers of dietary supplement products as a result of these regulations will mostly be passed on to consumers in the form of higher prices. Since consumer demand for dietary supplements is price elastic, most of the higher costs incurred by suppliers will be passed on to consumers. Consequently, higher dietary supplement prices will reduce real incomes for many consumers. However, the reduction in real incomes is thought to be more than offset by the benefits from these regulations. These benefits are measured as an improved ability by the FDA to respond to and contain threats of serious adverse health consequences from accidental contamination of dietary supplements.

National Productivity, Economic Growth, Job Creation, and Full Employment

Although this proposed regulation is significant, we do not expect it to substantially affect national productivity, growth, jobs, or full employment. The total costs will be small relative to the economy, and will be offset by benefits. The improved ability to respond to, and contain, serious adverse health consequences means less illness and fewer sick days taken by employees, and lower adjustment costs by firms that would otherwise need to hire replacement employees.

Exports

This proposed rule would require additional controls to be kept throughout the production and distribution chain for the manufacture of dietary ingredients and dietary supplements. The additional control costs would increase the total costs of production and distribution for all of the regulated products, including products sold within the U.S. and across national borders. These increased costs will be largely passed on to consumers in the form of higher prices, which will tend to reduce the quantity demanded of the regulated products. The increased prices of U.S. exports could reduce the quantity of U.S. exports demanded, particularly in comparison with exports from countries that do not implement similar regulations. We expect this effect to be insignificant, because under the proposed rule the increases in the price of United States exports (and resulting decreases in quantity demanded) would be quite small.

## VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We consulted with seven State officials to make a tentative determination about whether this proposed rule would have federalism implications. Based on this consultation, it does not appear that this proposed rule has federalism implications. In addition, we sent a letter on March 7, 2000, to elected State officials and their representative organization to notify them that our unified agenda was published on November 22, 1999, and identified this proposed CGMP rule as a rule that would publish in the year 2000. In that letter, we solicited comments on any federalism implications that this proposed rule may have. To date, no responses have been received to our solicitation. After publishing this proposed rule, FDA will send a letter to elected State officials and their representative organization requesting consultation about any federalism implications. We invite comment on our tentative determination that this proposed rule does not have federalism implications, and therefore, does not contain policies that have substantial direct effects on the States, or on the distribution of power and responsibilities among the various levels of government.

## IX. Request for Comments

Interested persons may submit to the Dockets Management Branch (*see* **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments to *http://www.fda.gov/dockets/ecomments* or two hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

## X. References

We have placed the following references on display in the Dockets Management Branch (*see* **ADDRESSES**). You may see them between 9 a.m. and 4 p.m., Monday through Friday.

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**List of Subjects**

*21 CFR Part 111*

Dietary foods, Drugs, Foods, Packaging and containers.

*21 CFR Part 112*

Drugs, Packaging and containers, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR chapter I, parts 111 and 112 as set forth below:

## PART 111—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

1. The authority citation for part 111 is revised to read as follows:

**Authority:** 21 U.S.C. 321, 342, 343, 348, 371, 374, 381, 393; 42 U.S.C. 264.

2. The part heading for part 111 is revised as set forth above.

3. Add new subpart A to part 111 to read as follows:

### Subpart A—General Provisions

Sec.



### Subpart A—General Provisions

#### § 111.1 Who is subject to these regulations?

You are subject to the regulations in this part if you manufacture, package, or hold a dietary ingredient or dietary supplement.

#### § 111.2 What are these regulations intended to accomplish?

The regulations in this part establish the minimum current good manufacturing practices that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement.

#### § 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in these regulations. For the purpose of these regulations, the following definitions also apply:

*Actual yield* means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement.

*Batch* means 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.

*Batch number, lot number, or control number* means 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.

*Component* means 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. Component includes ingredients and dietary ingredients as described in section 201(ff) of the Act.

*Consumer complaint* means 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 the regulations in this part, 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.

*Contact surface* means any surface that contacts a component, dietary ingredient, dietary supplement, and those surfaces from which drainage onto the component, dietary ingredient, dietary supplement, or onto surfaces that contact the component, dietary ingredient, or dietary supplement ordinarily occurs during the normal course of operations. Examples of contact surfaces include, but are not limited to, containers, utensils, tables, contact surfaces of equipment, and packaging.

*Ingredient* means any substance that is used in the manufacture of a dietary ingredient or dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the Act.

*Inprocess material* means 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.

*Lot* means 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 a 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.

*Microorganisms* means yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern. This definition includes, but is not limited to, species that:

(1) Have public health significance;

(2) Could cause a component, dietary ingredient, or dietary supplement to decompose;

(3) Indicate that the component, dietary ingredient, or dietary supplement is contaminated with filth; or

(4) Otherwise may cause the component, dietary ingredient, or dietary supplement to be adulterated.

*Must* is used to state mandatory requirements.

*Pest* means any objectionable insects or other animals including, but not limited to, birds, rodents, flies, mites, and larvae.

*Physical plant* means all or parts of a building or facility used for or in connection with manufacturing, packaging, or holding a dietary ingredient or dietary supplement.

*Quality control* means a planned and systematic operation or procedure for preventing a dietary ingredient or dietary supplement from being adulterated.

*Quality control unit* means any person or group that you designate to be responsible for quality control operations.

*Representative sample* means 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.

*Reprocessing* means 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.

*Sanitize* means 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.

*Theoretical yield* means 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.

*Water activity* ($a_w$) is 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.

*We* means the United States Food and Drug Administration (FDA).

*You* means a person who manufactures, packages, or holds dietary ingredients or dietary supplements.

### § 111.5 Do other statutory provisions and regulations apply?

In addition to the regulations in this part, you must comply with other applicable statutory provisions and regulations under the Act related to the manufacturing, packaging, or holding of dietary ingredients or dietary supplements.

### § 111.6 Exclusions.

The regulations in this part 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.

4. Add new subpart B to part 111 to read as follows:

## Subpart B—Personnel

Sec.

## Subpart B—Personnel

### § 111.10 What microbial contamination and hygiene requirements apply?

(a) *Microbial contamination.* You must 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, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. Such measures include, but are not limited to, the following:

(1) Excluding any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion, or any other abnormal source of microbial contamination, 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; and

(2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they have a health condition described in paragraph (a)(1) of this section that could contaminate any components, dietary ingredients, dietary supplements, or any contact surface.

(b) *Hygienic practices.* If you work in operations during which adulteration of the component, dietary ingredients, dietary supplement, or contact surface may occur, you must use hygienic practices to the extent necessary to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces. These hygienic practices include, but are not limited to:

(1) Wearing outer garments in a manner that protects against the contamination of components, dietary ingredients, dietary supplements, or any contact surface;

(2) Maintaining adequate personal cleanliness;

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:

(i) Before starting work; and

(ii) At any time when the hands may have become soiled or contaminated;

(4) 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 in which components, dietary ingredients, or dietary supplements are manipulated by hand. If hand jewelry cannot be removed, it must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, dietary ingredients, dietary supplements, or contact surfaces;

(5) Maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of an impermeable material;

(6) Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints;

(7) Not storing clothing or other personal belongings in areas where components, dietary ingredients, or dietary supplements or any contact surfaces are exposed or where contact surfaces are washed;

(8) 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

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

### § 111.12 What personnel qualification requirements apply?

(a) You must have qualified employees to manufacture, package, or hold dietary ingredients or dietary supplements; and

(b) Each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties.

### § 111.13 What supervisor requirements apply?

(a) You must assign qualified personnel to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements.

(b) You and the supervisors you use must be qualified by training and experience to supervise.

5. Add new subpart C to part 111 to read as follows:

**Subpart C—Physical Plant**

Sec.



## Subpart C—Physical Plant

### § 111.15 What sanitation requirements apply to your physical plant?

(a) *Physical plant facilities.* (1) You must maintain your physical plant in a clean and sanitary condition; and

(2) You must keep your physical plant in repair sufficient to prevent components, dietary ingredients, dietary supplements, or contact surfaces from becoming contaminated.

(b) *Cleaning compounds, sanitizing agents, and pesticides.* (1) You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use.

(2) You must 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 materials are necessary:

(i) To maintain clean and sanitary conditions;

(ii) For use in laboratory testing procedures;

(iii) For maintaining or operating the physical plant or equipment; or

(iv) For use in the plant's operations.

(3) You must 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, or contact surfaces.

(c) *Pest control.* (1) You must not allow animals or pests in any area of your physical plant. Guard or guide dogs are allowed in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary ingredients, dietary supplements, or contact surfaces;

(2) You must take effective measures to exclude pests from the physical plant and to protect against contamination of components, dietary ingredients, dietary supplements, and contact surfaces on the premises by pests; and

(3) You must not use insecticides, fumigants, fungicides, or rodenticides, unless you take precautions to protect against the contamination of components, dietary ingredients, dietary supplements, or contact surfaces.

(d) *Water supply.* (1) You must 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:

(i) Manufacturing dietary ingredients or dietary supplements;

(ii) Making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces;

(iii) Cleaning any surface; and

(iv) Employee bathrooms and hand-washing facilities.

(2) Water that contacts components, dietary ingredients, dietary supplements, or any contact surface must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements;

(3) You must have documentation or otherwise be able to show that water that contacts components, dietary ingredients, dietary supplements, or any contact surface meets the requirements in paragraph (d)(2) of this section.

(e) *Plumbing.* The plumbing in your physical plant must be of an adequate size and design and be adequately installed and maintained to:

(1) Carry sufficient amounts of water to required locations throughout the physical plant;

(2) Properly convey sewage and liquid disposable waste from your physical plant;

(3) Avoid being a source of contamination to components, dietary ingredients, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition;

(4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and

(5) Not allow backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary ingredients or dietary supplements, for cleaning contact surfaces, or for use in bathrooms or hand-washing facilities.

(f) *Sewage disposal.* You must dispose of sewage into an adequate sewage system or through other adequate means.

(g) *Bathrooms.* You must provide your employees with adequate, readily accessible bathrooms. The bathrooms must be kept clean and must not become a potential source of contamination to components, dietary ingredients, dietary supplements, or contact surfaces. You must:

(1) Keep the bathrooms in good repair at all times;

(2) Provide self-closing doors; and

(3) Provide doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination except where alternate means have been taken to protect against contamination (such as double doors or positive airflow systems).

(h) *Hand-washing facilities.* You must provide hand-washing facilities that are adequate, convenient, and furnish running water at a suitable temperature. You must do this by providing:

(1) Hand-washing and, where appropriate, hand-sanitizing facilities at each location in your physical plant where good hygienic practices require employees to wash or to sanitize or both wash and sanitize their hands;

(2) Effective hand-cleaning and sanitizing preparations;

(3) Air driers, sanitary towel service, such as disposable paper towels, or other suitable drying devices;

(4) Devices or fixtures, such as water control valves, designed and constructed to protect against recontamination of clean, sanitized hands;

(5) Signs that are easy to understand and are posted throughout the physical plant that direct employees handling components, dietary ingredients, dietary supplements, or contact surfaces to wash and, where appropriate, to sanitize their hands before they start work, after each absence from their duty station, and when their hands may have become soiled or contaminated; and

(6) 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.

(i) *Trash disposal.* You must convey, store, and dispose of trash to:

(1) Minimize the development of odor;

(2) Minimize the potential for the trash to attract, harbor, or become a breeding place for pests;

(3) Protect against contamination of components, dietary ingredients, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and

(4) Control hazardous waste to prevent contamination of components, dietary ingredients, dietary supplements, and contact surfaces.

(j) *Sanitation supervisors.* You must assign one or more employees to supervise overall sanitation. These supervisors must be qualified by training and experience to develop and supervise sanitation procedures.

**§ 111.20 What design and construction requirements apply to your physical plant?**

Any physical plant you use in the manufacture, packaging, or holding of dietary ingredients or dietary supplements must:

(a) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;

(b) Have adequate space for the orderly placement of equipment and holding 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;

(c) 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. Your physical plant must have and you must use separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components, dietary ingredients, and dietary supplements during the following operations:

(1) 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;

(2) 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;

(3) 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;

(4) Performing laboratory analyses and holding laboratory supplies and samples;

(5) Cleaning and sanitizing contact surfaces;

(6) Packaging and label operations; and

(7) Holding dietary ingredients or dietary supplements.

(d) Be designed and constructed in a manner that prevents contamination of

components, dietary ingredients, dietary supplements, or contact surfaces. The design and construction must include, but not be limited to:

(1) Floors, walls, and ceilings that are of smooth and hard surfaces that can be adequately cleaned and kept clean and in good repair;

(2) Fixtures, ducts, and pipes that do not contaminate components, dietary ingredients, dietary supplements, or contact surfaces by dripping or condensate;

(3) Adequate ventilation or environmental control equipment such as air flow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary ingredients, dietary supplements, or contact surfaces;

(4) 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;

(5) Equipment that controls temperature and humidity; and

(6) 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.

(e) Provide adequate light in:

(1) All areas where components, dietary ingredients, or dietary supplements are examined, processed, or held;

(2) All areas where contact surfaces are cleaned; and

(3) Hand-washing areas, dressing and locker rooms, and bathrooms.

(f) 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 of components, dietary ingredients, or dietary supplements in case of glass breakage.

(g) Provide protection by any effective means against contamination of components, dietary ingredients, and dietary supplements in bulk fermentation vessels, including consideration of:

(1) Use of protective coverings;

(2) Placement in areas where you can eliminate harborages for pests over and around the vessels;

(3) Placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and

(4) Use of skimming equipment.

(h) Use adequate screening or other protection against pests, where necessary.

6. Add new subpart D to part 111 to read as follows:

**Subpart D—Equipment and Utensils**

Sec.



## Subpart D—Equipment and Utensils

### § 111.25 What requirements apply to the equipment and utensils you use?

(a)(1) You must use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained. Equipment and utensils include, but are not limited to, the following:

(i) Equipment used to hold or convey;

(ii) Equipment used to measure;

(iii) Equipment using compressed air or gas;

(iv) Equipment used to carry out processes in closed pipes and vessels; and

(v) Equipment used in automatic, mechanical, or electronic systems.

(2) You must use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components, dietary ingredients, or dietary supplements with:

(i) Lubricants;

(ii) Fuel;

(iii) Coolants;

(iv) Metal or glass fragments;

(v) Filth or any other extraneous material;

(vi) Contaminated water; or

(vii) Any other contaminants.

(3) All equipment and utensils you use must be:

(i) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;

(ii) Corrosion-resistant if the equipment or utensils contact components, dietary ingredients, or dietary supplements;

(iii) Made of nontoxic materials;

(iv) Designed and constructed to withstand the environment of their intended use, the action of components, dietary ingredients, or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and

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

(4) Equipment and utensils you use must have seams that are smoothly bonded or maintained to minimize accumulation of component, dietary ingredient, or dietary supplement particles, dirt, filth, organic material, or any other extraneous materials or contaminants to minimize the opportunity for growth of microorganisms.

(5) Each freezer and cold storage compartment you use to hold components, dietary ingredients, or dietary supplements:

(i) Must be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that shows the temperature accurately within the compartment; and

(ii) Must have an automatic device for regulating temperature or an automatic alarm system to indicate a significant temperature change in a manual operation.

(6) Instruments or controls used in the manufacturing, packaging, or holding of a dietary ingredient or dietary supplement, including but not limited to, instruments or controls you use to measure, regulate, or record temperatures, hydrogen ion concentration (pH), water activity, or other conditions that control or prevent the growth of microorganisms or other contamination must be:

(i) Accurate and precise;

(ii) Adequately maintained; and

(iii) Adequate in number for their designated uses.

(7) Compressed air or other gases you introduce mechanically into or onto a component, dietary ingredient, dietary supplement, or contact surface or that you use to clean any contact surface must be treated in such a way that the component, dietary ingredient, dietary supplement, or contact surface is not contaminated.

(b)(1) You must calibrate instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement.

(2) You must calibrate before first use; and

(i) As specified in writing by the manufacturer of the instrument and control, or

(ii) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(c) You must:

(1) Establish a written procedure for calibrating instruments and controls you use in manufacturing or testing a

component, dietary ingredient, or dietary supplement and document that the written procedure was followed each time a calibration is performed, or

(2) Document at the time of performance that the instrument and control calibration established in accordance with this section was performed.

(d) You must identify the following for calibrating instruments and controls in any written procedure or at the time of performance:

(1) The instrument or control calibrated;

(2) The date of calibration;

(3) The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(4) The calibration method used including appropriate limits for accuracy and precision of instruments and controls when calibrating;

(5) The calibration reading or readings found; and

(6) The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(7) The initials of the person who performed the calibration.

(d) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

(e)(1) You must maintain, clean, and sanitize as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements. Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(2) You must ensure that all contact surfaces used for manufacturing or holding of low-moisture components, dietary ingredients, or dietary supplements are in a dry and sanitary condition at the time of use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.

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

(4) You must clean surfaces that do not touch components, dietary ingredients, or dietary supplements as frequently as necessary to protect against contaminating components, dietary ingredients, or dietary supplements.

(5) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be:

(i) Stored in appropriate containers; and

(ii) Handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface.

(6) Cleaning compounds and sanitizing agents must be adequate for intended use and safe under condition of use;

(7) You must store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and manner that protects them from contamination.

(f) You must keep calibration records as required by this section in accordance with § 111.125.

**§ 111.30 What requirements apply to automatic, mechanical, or electronic equipment?**

(a) When you use automatic, mechanical, or electronic equipment to manufacture, package, label, and hold a dietary ingredient or dietary supplement, you must:

(1) Design or select equipment to ensure that dietary ingredient or dietary supplement specifications are consistently achieved and

(2) Determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process.

(b) For any automatic, mechanical, or electronic equipment you use, you must:

(1) Routinely calibrate, inspect, or check to ensure proper performance. Your quality control unit must approve these calibrations, inspections, or checks;

(2) Make and keep written records of equipment calibrations, inspections, or checks;

(3) Establish and use appropriate controls, to ensure that your quality control unit approves changes in the master manufacturing record, batch control records, packaging operations and label operations, or changes to other operations related to the equipment that you use and that only authorized personnel institute the changes;

(4) Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by your quality control unit; and

(5) Make and keep backup file(s) of software programs and of data entered into your computer system. Your backup file (*e.g.,* a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered. You must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss.

(c) You must keep automatic, mechanical, or electronic equipment records required by this section in accordance with § 111.125.

**§ 111.50 [Redesignated as § 111.72 and Amended]**

7. Redesignate § 111.50 as § 111.72 and transfer it to a new subpart E, *Production and Process Controls,* and revise the section heading to read as follows:

**§ 111.72 What requirements apply to packaging of iron-containing dietary supplements?**

* * * * *

8. Add §§ 111.35 through 111.70 and § 111.74 to newly added subpart E to read as follows:

**§ 111.35 What production and process controls must you use?**

(a) You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary ingredients and dietary supplements.

(b) Your production and in-process control system must be designed to ensure that the dietary ingredient or dietary supplement is manufactured, packaged, and held in a manner that will prevent adulteration of the dietary ingredient or dietary supplement. The production and in-process control system must include all requirements of this subpart and must be reviewed and approved by the quality control unit.

(c) You must use a quality control unit in your manufacturing, packaging, and label operations for producing the dietary ingredient or dietary supplement to ensure that these operations are performed in a manner that prevents adulteration and ensures that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

(d) Any substance, other than a ''dietary ingredient'' within the meaning of section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act), the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement must be:

(1) Authorized for use as a food additive under section 409 of the Act; or

(2) Authorized by a prior sanction consistent with § 170.3(l) of this chapter; or

(3) If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement; or

(4) Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of section 201(ff) of the Act, must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement; and

(5) Must comply with all other applicable statutory and regulatory requirements under the Act.

(e) You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. Specifications must be established for:

(1) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;

(2) The in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;

(3) The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and

(4) The dietary ingredient or dietary supplement labels and the packaging that may come in contact with dietary ingredients and dietary supplements. The packaging must be safe and suitable for its intended use and comply with all other applicable statutory and regulatory requirements under the Act and must not be reactive or absorptive so as to affect the safety of the dietary ingredient and dietary supplement.

(f) You must monitor the in-process control points, steps, or stages to ensure that specifications established under paragraph (e) of this section are met and to detect any unanticipated occurrence that may result in adulteration;

(g) You must ensure, through testing or examination, that each specification that you established under paragraph (e) of this section is met. Specific testing requirements are as follows:

(1) You must test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met, provided that there are scientifically valid analytical methods available to conduct such testing.

(2) For any specification for identity, purity, quality, strength, or composition for which you document cannot be tested on the finished batch of a dietary ingredient or dietary supplement, because there is no scientifically valid analytical method available for such testing, then you must:

(i) Perform testing on each shipment lot of components, dietary ingredients or dietary supplements received to determine whether such specification is met; and

(ii) Perform testing in-process in accordance with the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements; and

(3) Your quality control unit must determine when finished batch testing cannot be completed for any specification on the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements.

(h) You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method.

(i) You must:

(1) Establish corrective action plans for use when an established specification is not met;

(2) Review the results of the monitoring required by this section and conduct a material review of any component, dietary ingredient, dietary supplement, packaging or label for which you establish a specification that is not met, or any unanticipated occurrence that adulterates or could result in adulteration of the component, dietary ingredient, dietary supplement, packaging, or label; and

(3) Make a material disposition decision for any component, dietary ingredient, dietary supplement, packaging, or label:

(i) If a component, dietary ingredient, dietary supplement, packaging, or label fails to meet specifications;

(ii) If any step established in the master manufacturing record is not completed;

(iii) If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label;

(iv) If calibration of an instrument or control suggests a problem that may have caused batches of a dietary ingredient or dietary supplement to become adulterated; or

(v) If a dietary ingredient or dietary supplement is returned.

(4) For any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label:

(i) You must reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence;

(ii) You must not reprocess a rejected component, dietary ingredient, or dietary supplement unless approved by the quality control unit; and

(iii) You must not reprocess any component, dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms or other contaminants, such as heavy metals;

(5) Have your quality control unit review and approve any material review and disposition decision described in paragraphs (i)(2) and (i)(3) of this section.

(j) The person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in paragraph (i) of this section. The documentation must be included in the appropriate batch production record and must:

(1) Identify the specific deviation from the specification or the unanticipated occurrence;

(2) Describe your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(3) Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration;

(4) Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence; and

(5) Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label.

(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following:

(1) Filth, insects, or other extraneous material;

(2) Microorganisms; and

(3) Toxic substances.

(l) Tests in accordance with this section must include at least one of the following:

(1) Gross organoleptic analysis;

(2) Microscopic analysis;

(3) Chemical analysis; or

(4) Other appropriate test.

(m) You must record results of all testing and examinations performed in accordance with this section. If a test or examination is performed on a batch production you must record the test or examination result in the batch production record in accordance with § 111.50(c)(10). Your records must document whether the testing and examination demonstrates that specifications are met.

(n) For any specification that is not met, you must conduct a material review and disposition decision under paragraph (i) of this section.

(o) You must make and retain records, in accordance with § 111.125, to ensure that you follow the requirements of this section. The records must include, but are not limited to:

(1) The specifications established;

(2) The actual results obtained during the monitoring operation;

(3) Any deviation from specifications and any unanticipated occurrences;

(4) Any corrective actions taken;

(5) The disposition decisions and followup; and

(6) The identity of the individual qualified by training and experience who investigated any deviation from specifications or unanticipated occurrence and the identity of the individual from the quality control unit who reviewed the results of that investigation.

#### § 111.37 What requirements apply to quality control?

(a) You must use a quality control unit to ensure that your manufacturing, packaging, label, and holding operations in the production of dietary ingredients and dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring that dietary ingredients and dietary supplements meet specifications for identity, purity, quality, strength, and composition.

(b) Your quality control unit must do the following:

(1) Approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, quality, strength, and composition of a dietary ingredient or dietary supplement;

(2) Determine whether all components, dietary ingredients, dietary supplements, packaging, and labels conform to specifications;

(3) Approve or reject all components, dietary ingredients, dietary supplements, packaging, and labels;

(4) Review and approve all master manufacturing records and all modifications to the master manufacturing records;

(5) Review and approve all batch production-related records which include, but are not limited to, cross referencing receiving and batch production records, approval of a material review and disposition decision, approval for reprocessing, and approval for releasing for distribution;

(6) Review and approve all processes for calibrating instruments or controls;

(7) Review all records for calibration of instruments, apparatus, gauges, and recording devices;

(8) Review all records for equipment calibrations, inspections, and checks;

(9) Review and approve all laboratory control processes, and testing results;

(10) Review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records, approval for repackaging and relabeling, and approval for releasing for distribution;

(11) Collect representative samples of:

(i) Each shipment lot of components, dietary ingredients, dietary supplements, packaging, and labels received to determine whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications;

(ii) Inprocess materials at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;

(iii) Each batch of dietary ingredient or dietary supplement manufactured to determine, before releasing for distribution, whether the dietary ingredient or dietary supplement meets its specifications for identity, purity, quality, strength, and composition; and

(iv) Each batch of packaged and labeled dietary ingredients or dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record.

(12) Keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. The reserve samples must:

(i) Be identified with the batch or lot number; and

(ii) Consist of at least twice the quantity necessary for tests.

(13) Perform appropriate tests and examinations of:

(i) Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications;

(ii) Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record where control is necessary to prevent adulteration;

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

(iv) Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record.

(14) Review and approve all material review and disposition decisions; and

(15) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

(c) Your quality control unit must establish and maintain written documentation at the time of performance that it performed the review, approval, or rejection requirements of this section by recording the following:

(1) Date the required review, approval, or rejection was performed; and

(2) Signature of the person performing the requirement.

(d) You must keep quality control records in accordance with § 111.125.

#### § 111.40 What requirements apply to components, dietary ingredients, dietary supplements, packaging, and labels you receive?

(a) For components, dietary ingredients, or dietary supplements you receive, you must:

(1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of the components, dietary ingredients, or dietary supplement;

(2) Visually examine the suppliers invoice, guarantee, or certification to ensure that the components, dietary ingredients, or dietary supplements are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met.

(3) Quarantine components, dietary ingredients, or dietary supplements until your quality control unit reviews the suppliers invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release the components, dietary ingredients, and dietary supplements from quarantine before you use them;

(4) Identify each lot of components, dietary ingredients, or dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component or dietary supplement, and the status (*e.g.,* quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment lot received; and

(5) Hold components, dietary ingredients, or dietary supplements under conditions that will protect against contamination, deterioration, and avoid mixups.

(b) For packaging and labels you receive, you must:

(1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of the packaging and labels;

(2) Quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met. You must conduct at least a visual identification on the containers and closures. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release packaging and labels from quarantine before you use them;

(3) Identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (*e.g.*, quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment lot received; and

(4) Hold packaging and labels under conditions that will protect against contamination, deterioration, and avoid mixups.

(c)(1) The person who performs the component, dietary ingredient, dietary supplement, packaging, or label requirements of this section must document, at the time of performance, that the requirements were followed. The documentation must include, but not be limited to:

(i) The date that the components, dietary ingredients, dietary supplements, packaging, or labels were received;

(ii) The signature of the person performing the requirement;

(iii) Any test results; and

(iv) Any material review and disposition decision you conducted in accordance with § 111.35(i) and disposition of any rejected material under § 111.74.

(2) You must keep component, dietary supplement, packaging, and label receiving records in accordance with § 111.125.

**§ 111.45 What requirements apply to establishing a master manufacturing record?**

(a) You must prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement that you manufacture and for each batch size to ensure uniformity from batch to batch. The master manufacturing record must:

(1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration; and

(2) Establish controls and procedures to ensure that each batch of dietary ingredient or dietary supplement manufactured meets those specifications.

(b) The master manufacturing record must include the following information:

(1) The name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;

(2) A complete list of components to be used;

(3) An accurate statement of the weight or measure of each component to be used;

(4) The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement in compliance with section 403(s) of the Federal Food, Drug, and Cosmetic Act;

(5) A statement that explains any intentional excess amount of a dietary ingredient;

(6) A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to prevent adulteration, and the expected yield when you finish manufacturing the dietary ingredient or dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is performed and material review is conducted and disposition decision is made;

(7) A description of packaging and a copy of the label to be used; and

(8) Written instructions including, but not limited to, the following:

(i) Specifications for each point, step, or stage in manufacturing the dietary ingredient or dietary supplement necessary to prevent adulteration;

(ii) Sampling and testing procedures;

(iii) Specific actions necessary to perform and verify points, steps, or stages, necessary to meet specifications and otherwise prevent adulteration, including, but not limited to, one person weighing or measuring a component and another person verifying the weight or measure and one person adding the component and another person verifying the addition;

(iv) Special notations and precautions to be followed; and

(v) Corrective action plans for use when a specification is not met.

(c) You must have the quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record.

(d) You must keep master manufacturing records in accordance with § 111.125.

**§ 111.50 What requirements apply to establishing a batch production record?**

(a) You must prepare a batch production record every time you

manufacture a batch of a dietary ingredient or dietary supplement and the batch production record must include complete information relating to the production and control of each batch.

(b) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in producing the batch.

(c) The batch production record must include, but is not limited to, the following information:

(1) The batch, lot, or control number;

(2) Documentation at the time of performance, showing the date on which each step of the master manufacturing record was performed, and the initials of the persons performing each step, including but not limited to:

(i) The person responsible for weighing or measuring each component used in the batch; and

(ii) The person responsible for adding the component to the batch.

(3) The identity of equipment and processing lines used in producing the batch;

(4) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch;

(5) The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;

(6) The identity and weight or measure of each component used;

(7) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the weight or measure of each component used in the batch;

(8) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the addition of components to the batch;

(9) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(10) The actual test results for any testing performed during the batch production;

(11) Documentation that the dietary ingredient and dietary supplement meets specifications;

(12) Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;

(13) Any documented material review and disposition decision in accordance with § 111.35(j); and

(14) Signature of the quality control unit to document batch production record review and any approval for reprocessing or repackaging.

(d) The quality control unit must review in accordance with § 111.37(b)(5) the batch production record established in paragraph (c) of this section.

(1) If a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record.

(2) The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.

(e) The quality control unit must document in accordance with § 111.37(c) the review performed in accordance with paragraph (d) of this section and it must be documented at the time of performance. The review and documentation must include, but is not limited to, the following:

(1) Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results;

(2) Identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master production record;

(3) Records of investigations, conclusions, and corrective actions performed in accordance with paragraph (d) of this section; and

(4) The identity of the person qualified by training and experience who performed the investigation in accordance with paragraph (d) of this section.

(f) You must not reprocess a batch that deviates from the master manufacturing record unless approved by the quality control unit. You must not reprocess a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals;

(g) Any batch of dietary ingredient or dietary supplement that is reprocessed must meet all specifications for the batch of dietary ingredient or dietary supplement and be evaluated and approved by the quality control unit before releasing for distribution. The results of the reevaluation by the quality control unit must be documented in the batch production record;

(h) You must collect representative reserve samples of each batch of dietary ingredient or dietary supplement and keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine whether, for example, the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition; and

(i) You must keep batch production records in accordance with § 111.125.

### § 111.60 What requirements apply to laboratory operations?

(a) You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine that components, dietary ingredients, and dietary supplements received meet specifications; that specifications are met during in-process, as specified in the master manufacturing record; and that dietary ingredients and dietary supplements manufactured meet specifications.

(b)(1) You must establish and follow laboratory control processes that are approved by the quality control unit. Laboratory control processes must include, but are not limited to, the following:

(i) Use of criteria for selecting appropriate examination and testing methods;

(ii) Use of criteria for establishing appropriate specifications; and

(iii) Use of sampling plans for obtaining representative samples of:

(A) Components, dietary ingredients, and dietary supplements received to determine whether specifications are met;

(B) In-process materials during the batch manufacturing when testing or examination is required in the master manufacturing record;

(C) Each batch of dietary ingredient or dietary supplement manufactured to determine that the dietary ingredient or dietary supplement meets specifications;

(D) Packaging and labels received to determine that the materials meet specifications; and

(E) Each batch of packaged and labeled dietary ingredients or dietary supplements to ensure that the label specified in the master manufacturing record has been applied.

(iv) Use of criteria for selecting standard reference materials used in performing tests and examinations;

(v) Use of appropriate test method validations; and

(vi) Use of test methods and examinations in accordance with established criteria.

(2) The person who conducts the testing and examination at the time of

performance, must document that laboratory methodology established in accordance with this section is followed. The documentation must include the testing and examination results.

(3) You must keep laboratory examination and testing records in accordance with § 111.125.

(c) You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.

(d) You must identify and use the appropriate validated testing method for each established specification for which testing is required to determine whether the specification is met.

**§ 111.65 What requirements apply to manufacturing operations?**

(a) You must design or select manufacturing processes to ensure that dietary ingredient or dietary supplement specifications are consistently achieved.

(b) You must conduct all manufacturing operations in accordance with adequate sanitation principles.

(c) You must take all the necessary precautions during the manufacture of a dietary ingredient or dietary supplement to prevent contamination of components, dietary ingredients, or dietary supplements. These precautions include, but are not limited to:

(1) Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination;

(2) Washing or cleaning components that contain soil or other contaminants;

(3) Using water that meets the National Primary Drinking Water regulations or, where necessary, higher sanitary quality and that complies with all applicable Federal, State, and local regulations for water that is used in the manufacturing operation. If you reuse water that was used to wash components to remove soil or contaminants, the reused water must be safe and of adequate sanitary quality so that it does not become a source of contamination;

(4) Performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components, dietary ingredients, and dietary supplements;

(5) Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity ($a_w$), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition;

(6) Holding components, dietary ingredients, and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components, dietary ingredients, and dietary supplements from becoming adulterated;

(7) Identifying and holding any components, dietary ingredients, or dietary supplements, for which a material review and disposition decision is required, in a manner that protects the components, dietary ingredients, or dietary supplements against contamination and mixups;

(8) Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary ingredients or dietary supplements against contamination. Such steps must include consideration of:

(i) Cleaning and sanitizing contact surfaces;

(ii) Using temperature controls; and

(iii) Using time controls.

(9) Using effective measures to protect against the inclusion of metal or other foreign material in components, dietary ingredients, or dietary supplements. Compliance with this requirement must include consideration of the use of:

(i) Filters or strainers;

(ii) Traps;

(iii) Magnets; or

(iv) Electronic metal detectors.

(10) Segregating and identifying all containers for a specific batch of dietary ingredients or dietary supplements to identify their contents and, where necessary, the phase of manufacturing; and

(11) Identifying all processing lines and major equipment used during manufacturing to indicate their contents including the name of the dietary ingredient or dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing.

(d) You must conduct a material review and make a disposition decision in accordance with § 111.35(i) for any component, dietary ingredient, or dietary supplement that fails to meet specifications or that is or may be adulterated. If the material review and disposition decision allows you to reprocess the component, dietary ingredient, or dietary supplement, you must retest or reexamine the component, dietary ingredient, or dietary supplement to ensure that it meets specifications and is approved by the quality control unit.

**§ 111.70 What requirements apply to packaging and label operations?**

(a) You must take necessary actions to ensure that each packaging container for holding dietary ingredients or dietary supplements meets specifications so that the condition of the packaging container will not contaminate your dietary ingredients or dietary supplements nor cause them to deteriorate;

(b) You must fill, assemble, package, and perform other related operations in a way that protects your dietary ingredients or dietary supplements against adulteration and misbranding. You must do this using any effective means, including but not limited to, the following:

(1) Cleaning and sanitizing all filling and packaging equipment, utensils, and dietary ingredient or dietary supplement containers, as appropriate;

(2) Protecting manufactured dietary ingredients and dietary supplements from contamination, particularly airborne contamination;

(3) Using sanitary handling procedures;

(4) Establishing physical or spatial separation of packaging and labels from operations on other dietary ingredients and dietary supplements to prevent mixups;

(5) Identifying, by any effective means, filled dietary ingredient or dietary supplement containers that are set aside and held in unlabeled condition for future label operations, to prevent mixups;

(6) Identifying the dietary ingredient or dietary supplement with a batch, lot, or control number that can be used to determine the manufacturing history and control of the batch;

(7) Examining a representative sample of each batch of the packaged and labeled dietary ingredient or dietary supplement to ensure that the dietary ingredient or dietary supplement meets specifications and that the label specified in the master manufacturing record has been applied; and

(8) Suitably disposing of labels and other packaging for dietary ingredients or dietary supplements that are obsolete or incorrect to ensure that they are not used in any future packaging and label operations.

(c) You must conduct a material review and make a disposition decision of any packaged and labeled dietary ingredients or dietary supplements that do not meet specifications.

(d) You must only repackage or relabel dietary ingredients or dietary supplements after the quality control unit has approved and documented such repackaging or relabeling.

(e) You must retest or reexamine any repackaged or relabeled dietary ingredients or dietary supplements. They must meet all specifications and

the quality control unit must approve or reject their release for distribution.

(f)(1) You must control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies; and

(2) You must examine, before packaging operations, packaging and labels for each batch of dietary ingredient or dietary supplement to ensure that the label and packaging conform to the master manufacturing record.

(g) The person that performs the requirements of this section must document at the time of performance that the requirements are performed including, but not limited to, documentation in the batch production record of:

(1) The identity and quantity of the packaging and labels used and reconciliation of any discrepancies between issuance and use;

(2) The examination conducted in accordance with paragraph (b)(7) of this section;

(3) The conclusions you reached from retests conducted in accordance with paragraph (e) of this section; and

(4) Any material reviews and disposition decisions for packaging and labels.

(h) You must keep packaging and label operations records required under this section in accordance with § 111.125.

#### § 111.74 What requirements apply to rejected components, dietary ingredients, dietary supplements, packaging, and labels?

You must clearly identify, hold, and control under a quarantine system any component, dietary ingredient, dietary supplement, packaging, and label that is rejected and unsuitable for use in manufacturing, packaging, or label operations.

9. Add subpart F to part 111 to read as follows:

### Subpart F—Holding and Distributing

Sec.



### Subpart F—Holding and Distributing

#### § 111.80 What requirements apply to holding components, dietary ingredients, dietary supplements, packaging, and labels?

(a) You must hold components, dietary ingredients, and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, quality, strength, and composition of the components, dietary ingredients, and dietary supplements are not affected.

(b) You must hold packaging and labels under appropriate conditions of temperature, humidity, and light so that the quality of the packaging and labels are not affected.

(c) You must hold components, dietary ingredients, dietary supplements, packaging, and labels under conditions that do not lead to the mixup, contamination, or deterioration of components, dietary ingredients, dietary supplements, packaging, and labels.

#### § 111.82 What requirements apply to holding in-process material?

(a) You must identify and hold in-process material under conditions that will protect them against mixup, contamination, and deterioration.

(b) You must hold in-process material under appropriate conditions of temperature, humidity, and light.

#### § 111.83 What requirements apply to holding reserve samples of components, dietary ingredients, and dietary supplements?

(a) For any reserve samples of components or dietary ingredients you collect, you must hold such reserve samples in a manner that protects against contamination and deterioration.

(b) You must hold reserve samples of dietary supplements in a manner that protects against contamination and deterioration. This includes, but is not limited to:

(1) Holding the reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use; and

(2) Using the same container-closure system in which the dietary supplement is marketed or in one that provides the same level of protection against contamination or deterioration.

#### § 111.85 What requirements apply to returned dietary ingredients or dietary supplements?

(a) You must identify and quarantine returned dietary ingredients or dietary supplements until the quality control unit conducts a material review and makes a disposition decision.

(b) You must not salvage returned dietary ingredients and dietary supplements, unless:

(1) Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions; and

(2) Tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition.

(c) You must destroy or suitably dispose of the returned dietary ingredients or dietary supplements if such dietary ingredients or dietary supplements do not meet specifications for identity, purity, quality, strength, and composition, unless the quality control unit conducts a material review and makes a disposition decision to allow reprocessing.

(d) If the reason for a dietary ingredient or a dietary supplement being returned implicates associated batches, you must conduct an investigation of your manufacturing processes and those other batches to determine compliance with specifications.

(e) You must establish and keep records for this section on the material review and disposition decision and any testing conducted to determine compliance with established specifications in the master manufacturing record for the type of dietary ingredient or dietary supplement that was returned.

(f) You must keep returned dietary ingredient and dietary supplement records in accordance with § 111.125.

#### § 111.90 What requirements apply to distributing dietary ingredients or dietary supplements?

Distribution of dietary ingredients and dietary supplements must be under conditions that will protect the dietary ingredients and dietary supplements against contamination and deterioration.

10. Add subpart G to part 111 to read as follows:

### Subpart G—Consumer Complaints

#### § 111.95 What requirements apply to consumer complaints?

(a) A qualified person must review all consumer 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 specifications and other requirements that, if not met, may result in a possible risk of illness or injury.

(b) Your quality control unit must review all consumer complaints involving the possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a possible risk of illness or injury, to determine whether there is a need to investigate the consumer complaint.

(c) Your quality control unit must investigate a consumer complaint when there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event.

(d) Your quality control unit's investigation of a consumer complaint must include the batch records associated with the dietary ingredient or dietary supplement involved in the consumer complaint. Your quality control unit must extend the investigation to other batches of dietary ingredients or dietary supplements that may have been associated with an adverse event.

(e) You must make and keep a written record of every consumer complaint that is related to good manufacturing practices. For the purposes of the regulations in this part, 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. The consumer complaint written record must include, but is not limited to, the following:

(1) The name and description of the dietary ingredient or dietary supplement;

(2) The batch or lot number of the dietary supplement, if available;

(3) The name of the complainant, if available;

(4) The nature of the complaint including how the consumer used the product;

(5) The reply to the complainant, if any; and

(6) Findings of the investigation and followup action taken when an investigation is performed.

(f)(1) The person who performs the requirements in accordance with this section must document at the time of performance that the requirement was performed.

(2) You must keep consumer complaint records in accordance with § 111.125.

11. Add subpart H to part 111 to read as follows:

## Subpart H—Records and Recordkeeping

### § 111.125 What requirements apply to recordkeeping?

(a) You must keep written records required by this part for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with those records.

(b) Records required under this part must be kept as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records. If you use reduction techniques, such as microfilming, you must make suitable reader and photocopying equipment readily available to FDA. All electronic records must comply with part 11 of this chapter.

(c) You must have all records required under this part, or copies of such records, readily available during the retention period for authorized inspection and copying by FDA when requested.

12. Part 112 is added to read as follows:

## PART 112—RESTRICTIONS FOR SUBSTANCES USED IN DIETARY SUPPLEMENTS

**Subpart A—General Provisions [Reserved]**

**Subpart B—New Dietary Ingredients [Reserved]**

**Subpart C—Restricted Dietary Ingredients [Reserved]**

**Authority:** 21 U.S.C. 321, 342, 343, 371.

Dated: January 29, 2003.

**Mark B. McClellan,**

*Commissioner of Food and Drugs.*

Dated: January 29, 2003.

**Tommy G. Thompson,**

*Secretary of Health and Human Services.*

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