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 propose § 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 propose § 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 and 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 ccmpound 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 persons 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 results 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 www.fda.gov, or using the interactive form available on the MedWatch Internet site at 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	No. 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

Table 1.--Estimated Annual Recordkeeping Burden[1] (Continued)

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
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.