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 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.

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. 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;

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

- Show that your quality control unit approved the material disposition decision.

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. 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. 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;

- 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; 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 requirements established in accordance with proposed § 111.37 by recording the date when the requirement was performed, the signature of the person performing the requirement, and the results of any test and examination performed. Furthermore, you would be required to keep quality control records. 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. Further, we invite comment on whether there are procedures, other than those discussed, that we should include in a final rule.

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). The written procedures, that you should consider include those for:

- Receipt;
- Identification;
- Holding;
- Sampling;
- Examination and testing;
- Material review and disposition decision, including the approval or rejection of the component, dietary ingredient, dietary supplement, packaging, or labels; and
- Release of component, dietary ingredient, dietary supplement, packaging, or labels for use.

We invite comment on whether these procedures or others not discussed should be considered for inclusion in a final rule.

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. 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.

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, and whether there are other procedures that we should include in a final rule.

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;
- 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 of the person responsible for weighing or measuring each component used in the batch and the initials of the person verifying the weight or measure;
- The initials of the person responsible for adding the components to the batch and the initials of the person verifying the addition;
- 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;

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

- Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results;
- Identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master manufacturing record;

- Records of investigations, conclusions, and corrective actions performed in accordance with proposed § 111.50(d); and
- The identity of the person qualified by training and experience who performed the investigation in accordance with proposed § 111.50(d).

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

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

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

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

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

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

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

Proposed § 111.60(b)(1) would require that you establish and follow laboratory control processes that the quality control unit

has approved. For example, under proposed § 111.60(b)(1)(i) and (b)(1)(ii), the laboratory control processes would include use of criteria for selecting appropriate testing and examination methods and for establishing appropriate specifications. Specifications play an important role in CGMP's because they may help determine whether a dietary ingredient or dietary supplement is adulterated.

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

Similarly, criteria for selecting appropriate test and examination methods include parameters such as type of tests and examinations needed based on the component you receive. For example, you might use morphological characters and organoleptic characteristics in some cases to identify botanical dietary ingredients at the time of collection or for unprocessed botanicals. When sufficient morphological characters are present to separate the plant species from other plant species, an accurate identification can be made since morphological

characters are the sole basis of distinguishing most of the world's plant species. However, unprocessed botanicals that do not contain all the plant parts necessary to include adequate morphological characters to assure the correct species should have other identity aids or tests to assure the identity of the botanical. It is possible to use only a picture as an identity standard for whole fresh Ginkgo leaf from a cultivated field because the Ginkgo leaf is not easily confused with the leaf shape, venation, and color of other leaves that could be present in the field. In contrast, powdered Ginkgo leaf is a different form of the dietary ingredient and would require microscopic and/or chemical analysis. Ginkgo extracts have no morphological or anatomical features, and it is possible that extracts may include a number of chemical compounds at different ratios and concentrations that would require a different chemical test to assure the identity of the dietary ingredient. Botanical dietary ingredients that come from wild rather than cultivated sources may grow among and be unintentionally harvested with "poisonous" plants; therefore, an identity test also would need to show whether a botanical dietary ingredient is adulterated with another substance or a poisonous plant.

To illustrate this point, a specification may contain a simple identity test, and these tests may show whether a dietary ingredient is adulterated with another substance or is a poisonous plant that should not be ingested. Misidentification

or a mixup of botanical ingredients can cause a product to be adulterated (Refs. 6 and 69 through 73). Heavy metals may contaminate botanical and natural-occurring ingredients if a plant is grown and harvested in an area contaminated with heavy metals or even processed in a contaminated area (Refs. 74 and 75). Pesticides also may contaminate botanical ingredients; this occurs in rural areas where the botanical plant grow alongside commercial crops (Ref. 64). Therefore, you must consider what criteria you need to include for the types of testing that are needed, for example, for heavy metal or pesticide contamination, or identity testing criteria for selecting appropriate test methods, for example, whether to use organoleptic or chemical analyses for identity testing. In addition, you must establish criteria for specifications for the tests and examinations used. Establishing such criteria for specifications and appropriate test and examination methods will provide you with internal processes that will help prevent misidentification and contamination.

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

- Components, dietary ingredients, and dietary supplements received;

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

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

to your discretion so that you can develop a sampling plan that suits your products and your testing needs.

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

- Use of criteria for selecting standard reference materials used in performing tests and examinations. An authenticated plant reference material may be used as standard reference material in performing certain organoleptic examinations. An authenticated plant reference material is material that has been authenticated as the correct plant species and correct plant part(s) by a qualified plant taxonomist. As described earlier in this document, an organoleptic examination may be an appropriate examination to confirm plant identity when sufficient morphological characters are present to separate the plant species from other plant species. For microscopic and chemical tests, a reference material is a highly purified compound that is well characterized, and you would use the reference material to perform tests including calibration tests. In general, there are two types of reference materials: (1) Compendial reference standards that do not require characterization; and (2) noncompendial standards. Noncompendial standards should be of the highest purity that can be obtained by

reasonable effort and should be thoroughly characterized to assure their identity, purity, quality, and strength. Ideally, you should use compendial reference standards whenever possible, but if no compendial reference standard exists, you should establish appropriately characterized inhouse materials prepared from representative lots;

- Use of appropriate test method validations. Test method validation determines whether a newly-developed or existing test method is accurate, precise, and specific for its intended purpose. We have discussed previously the terms "accurate" and "precise." Validation involves evaluating the test method on multiple occasions or in multiple test facilities. Official methods, such as AOAC International methods, are validated in collaborative studies using several laboratories under identical conditions. The AOAC International methods that are validated in collaborative studies often are often cited as "official validated methods." If you modify an officially validated method, you should document the reason for the modification and have data to show that the modified method produced results that are at least as accurate and reliable as the established method for material being tested. Further, you should have

complete records of any testing and standardization of laboratory reference standards, reagents, and standard solutions that you use in your laboratory operations. Proposed § 111.25(b)(1) would require calibration of laboratory instruments, apparatus, gauges, and recording devices. Validated methods also exist in official compendia for vitamins, minerals, and several botanicals, so you should use validated methods whenever available. You may use validated methods that can be found in official references, such as AOAC International, USP and others.

Other method validations are conducted using two or three laboratories or in a single laboratory by repeating the same test multiple times. Official and nonofficial method validations use similar performance parameters in conducting method validations. If an official validated method does not exist in an official reference, the method you use may be validated by using multiple tests at your laboratory or multiple laboratories performing the same test to document that the intended use of the method is consistently fulfilled. You must validate that the official or nonofficial method works under your conditions of use in your setting. You also should conduct day-to-day validations of the method that you use, whether it is

an official validated method or a less-formal validated method, under the conditions of use to ensure that the method will provide the information you need to ensure that your dietary ingredient or dietary supplement has the identity, purity, quality, strength, and composition that it is supposed to have and is thus not adulterated. Consistent, day-to-day test recoveries for the reference material are one indicator that the analytical method is working. There are at least two references that describe test method validation performance parameters: (1) Performance parameters for chromatographic methods are described in "Reviewer Guidance, Validation of Chromatographic Methods" (Center for Drug Evaluation and Research, FDA, November 1994) (Ref. 76); and (2) International Conference on Harmonisation (ICH); Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (63 FR 31506, June 9, 1998); and

- Use of test methods in accordance with established criteria. Your process for performing test methods criteria must include sufficient detail, including the material you are testing, the purpose of the test, and the test method. The description of the test method criteria must include any reagents used and preparation

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

you would be able to evaluate what the most appropriate test would be for the component, dietary ingredient, or dietary supplement and to use the test methods that are suited to your products and your manufacturing needs. Your test methodology must be specific for the component, dietary ingredient, or dietary supplement and the specifications you have established.

Proposed § 111.60(b)(2) and (b)(3) would apply to documentation and recordkeeping for your laboratory operations. Proposed § 111.60(b)(2) would require the 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. In addition, we invite comment on whether there are other procedures that we should include in a final rule.

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.

Proposed § 111.65(e) would require that person who performs the material review and disposition review required in accordance with this section to document at the time of performance the results of the material review and disposition decision and such documentation must be maintained with the batch production record. The document must include but not be limited to the date and time the requirement was performed and the signature of the person that performed the procedure. Proposed § 111.65(e) also would require that you keep these manufacturing operation records in accordance with proposed § 111.125. Maintaining the manufacturing operations 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 we should require, in a final rule, that you establish and follow written procedures to implement the manufacturing operations required in proposed § 111.65, and whether there are other procedures that we should include in a final rule.

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. We invite comment on whether there are other procedures, that we should include in a final rule.

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 and whether there are other procedures that we should include in a final rule.

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 and whether there are other procedures that we should include in a final rule.

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.