FDA/CFSAN's Responses to OMB's Comments Proposal Inserts Dietary Supplement CGMP Proposed Rule January 13, 2003

dietary ingredients. Likewise, further study is needed for some dietary ingredients before dissolution, disintegration, bioavailability, expiration dating, or other quality standard requirements can be proposed.

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

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

F. Proposal Highlights and Requests for Comments

This proposed rule is intended to ensure that manufacturing practices will not result in an adulterated dietary supplement and that supplements are properly labeled. This proposed rule, if finalized as proposed, will give consumers greater confidence that the dietary supplements they choose to use will have the identity, strength, purity, quality, or composition claimed on the label. Insert # 20

We propose requirements for: (1) Personnel, (2) the physical plant environment, (2) equipment and utensils, (3)

Page 35 Insert #20:
A manufacturer of a dietary ingredient or a dietary supplement cannot make claims that state or imply that the dietary ingredient or dietary supplement is safe and/or effective simply because it has been manufactured in compliance with current good manufacturing practice (CGMP) requirements. However, we believe that a voluntary labeling statement about the fact that a dietary ingredient or dietary supplement has been made in compliance with CGMP requirements might be made lawfully under the act, provided that such a statement is made in an appropriate context and with adequate disclaimers so that consumers fully understand it and are not misled by it. The proposed rule governing CGMP requirements for dietary supplements address manufacturing controls to ensure that dietary ingredients and dietary supplements are produced in a manner that will not adulterate or misbrand such products. Compliance with any final rule, based on the proposal, will not ensure that the dietary ingredient or dietary supplement itself is safe or effective. Thus, the agency believes that an unqualified statement saying simply "produced in compliance with dietary supplement current good manufacturing practice requirements," without more, could well suggest that a product may be safe and effective or somehow superior to other dietary ingredient and dietary supplement products that are subject to the same CGMP requirements. Such a statement would likely be considered misleading by FDA under sections 403(a)(1) and 201(n) of the act. We believe however, that it might be possible to cure an unqualified statement by including language clarifying to consumers that all dietary ingredients and dietary supplements must be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary ingredient or dietary supplement is safe or effective. As usual, the manufacturer would be responsible for ensuring that any such voluntary labeling statements on its dietary ingredient and dietary supplement products are truthful and not misleading. The agency would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

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

Insert #1 →

We seek comment on whether certain additional provisions should be included as requirements in a final rule. For example, we invite comment on whether a final rule should include a requirement for certain personnel records; for written procedures in a number of areas; for equipment verification; for additional testing of incoming ingredients; and for expiration dating and related testing. Insert #2 We also seek comment on whether this rule should include specific requirements for the use of animal-derived dietary ingredients, and requirements for persons who handle raw agricultural commodities. Specific requests for comment of this type are contained below in relevant sections of this preamble.

II. General Issues

A. Legal Authority

We are proposing these regulations under sections 201, 393, 409, 701(a), 704, and 801 of the act (21 U.S.C. 321, 903, 348,

Page 39 Insert #1:
CGMP records document the manufacturer's operation throughout time and are essential to an enforceable regulation. Because FDA does not observe the manufacturer's operation fulltime, records can ensure that the FDA has the information needed to identify noncompliance and to bring a non-compliant manufacturer into compliance. Records can show that appropriate monitoring is performed, pinpoint with confidence when a deviation began and ended, and prove that required quality control measures and practices were performed as often as necessary to ensure control. Review of manufacturing records with sufficient frequency can ensure that any problems are uncovered promptly and can facilitate prompt modification, have an impact on the production of subsequent batches of the product, and prevent introduction of potentially hazardous dietary supplements into the market place. Review of consumer complaint records can facilitate the identification of trends in reports of illness or injury, identify related batch records to identify previously undetected manufacturing deviation, and have an impact on the prompt recall of any potentially hazardous dietary supplement.

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

Although records are not required in 21 CFR Part 110, CGMPs in manufacturing, packing, or holding human food, records are required in the other commodity-driven food CGMPs (i.e., 21 CFR Part 129, Processing and bottling of bottled drinking water; 21 CFR 120, Hazard Analysis and Critical Control Point (HAACP) Procedures for the Safe and Sanitary

Processing and Importing of Juice; 21 CFR Part 123, Fish and fishery products; 21 CFR Part 106 Infant formula quality control procedures; and 21 CFR Part 113, Thermally processed low-acid foods packaged in hermetically sealed containers). Further, records are included in the CGMPs submitted to FDA by industry, the National Nutritional Foods Association Standards, the NSF International draft standards (Ref. 83), and the USP draft Manufacturing Practices for Dietary Supplements.

Page 39 Insert #2:
Written procedures are included in the dietary supplement CGMP outline submitted to FDA by industry, National Nutritional Foods Association standards, the NSF International draft standards, and the USP draft Manufacturing Practices. In order to limit the burden to manufacturers, FDA is not proposing to require written procedures. However, FDA is proposing that manufacturers maintain appropriate records to ensure the identity, purity, quality, strength, and composition of a given product and records that are necessary for efficient enforcement and to permit trace back. Although we have not proposed requirements for written procedures as did these other groups, we seek comment on whether such practices should be included in a final rule. Later in this document, we request comments on specific written procedures and describe FDA's current thinking concerning what could be included in such a written procedure.

associations. The majority of comments responded both to the nine questions we asked in the ANPRM and on certain provisions in the industry outline. We also address the comments on the nine questions in section II.B of this document. We discuss significant comments about certain provisions in the industry outline in our discussion of related proposed requirements.

Included with its comments to the ANPRM, the United States Pharmacopeia (USP) submitted a copy of its general chapter, "Manufacturing Practices for Nutritional Supplements," (Ref. 2) and in March/April 2002, USP proposed revisions to this general chapter to introduce provisions pertaining to botanical preparations (Ref. 82). In February 2000, we received a copy of the National Nutritional Foods Association's (NNFA) "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" (Ref. 3). We found that the industry outlines published in the ANPRM, the USP manufacturing practices, and the NNFA standards were useful in developing this proposed rule. We included certain provisions found in these outlines in this CGMP proposed rule. These three outlines indicate that dietary ingredient and dietary supplement manufacturers already recognize that there are basic, common steps needed to manufacture a dietary ingredient or dietary supplement that is not adulterated. For example, these practices include requirements for:

Insert #3

Page 12 Insert #3:
although, as established in the regulatory impact analysis, a large percentage of manufacturers do not follow a good manufacturing model.

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

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

CGMP regulations for dietary supplements might also benefit some establishments in the industry, although we cannot be certain about the magnitude or the incidence of the benefits. Manufacturers may not always have sufficient private incentives to adopt good manufacturing practices, but when they do so, they

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might increase their efficiency over time. By controlling their manufacturing practices, dietary ingredient and dietary supplement manufacturers can reduce manufacturing errors, the number of consumer complaints and product returns due to quality, the number of rejected batches, equipment downtime, and increase their productivity which offsets some of the cost of adopting the controls.

Additionally, a CGMP rule would create uniform minimum standards for manufacturers that would apply to all dietary ingredient and dietary supplement manufacturers. All manufacturers would have to meet the same CGMP requirements, so no manufacturer would gain an economic advantage by using substandard manufacturing, packaging, or holding standards or by not observing any good manufacturing, packaging, or holding practices. Having uniform standards might increase general consumer demand for these products due to increased consumer confidence in their quality, although we cannot be certain this will happen.

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

In developing this proposed rule, we were careful not to propose requirements that are not technically feasible to meet. In some areas where there has been scientific study but where the science is still evolving, the proposal recognizes the evolving state of the science, but would give you maximum flexibility in

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supplements that may not be marketed or sold in the United States and that are exported under section 801(e) of the act.

In addition to having the authority under the act to require recordkeeping, we also have authority to require access to the records. Because the practices set forth in the proposed CGMP rule are necessary to providing consumers with dietary supplements that are not adulterated, access to records that demonstrate that firms follow CGMPs is essential to confirming systematic compliance with CGMPs. We also have the authority to copy the records when necessary. We may consider it necessary to copy records when, for example, our investigator may need assistance in reviewing a certain record from relevant experts in headquarters. If we were unable to copy the records, we would have to rely solely on our inspector's notes and reports when drawing conclusions. A failure to have a required record would mean that a food is adulterated under section 402(g) of the act.

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

~~manufacturers~~ because the manufacturer can recall its products that may be adulterated or misbranded more quickly.

B. Issues From the ANPRM

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

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

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

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

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

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have used the terms "component, dietary ingredient, or dietary supplement" instead of food, and we have added several examples of contact surfaces. The proposed definition would include the inside of containers.

Proposed § 111.3 defines "ingredient" as "any substance that is used in the manufacture of a dietary ingredient or a dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement." The proposed definition would explain that an ingredient "includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the act." Thus, under proposed § 111.3, an "ingredient" may be a substance that is present in the finished dietary ingredient or dietary supplement that is intended to have some activity (such as a vitamin, mineral, or amino acid), but could also be a substance that is not intended to have any activity (such as the gelatin used to make the capsule holding the dietary ingredients). This proposed definition and the proposed definition for "component" in proposed § 111.3 differ in that "component" includes the various materials used to manufacture a dietary supplement that may not appear in the final product. Insert #22

Proposed § 111.3 defines "in-process material" as "any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary ingredient or dietary supplement." In-process material

Page 100, Insert #22:
Because an ingredient is defined as a substance that is intended to be present in the finished dietary ingredient or dietary supplement and a component is defined as a substance that may or may not be included in the finished dietary ingredient or dietary supplement, all ingredients are components but not all components are ingredients.

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requests comments on whether all contact surfaces should be subject to proposed § 111.3 "sanitize."

Proposed § 111.3 defines "theoretical yield" as "the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production." We would complement this definition by defining "actual yield" in proposed § 111.3 as "the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement." Comparing theoretical yields to actual yields may help identify deviations or problems in the manufacturing or packaging process. To illustrate this point, you should understand that the theoretical yield is the quantity or amount that you expect to see at a particular step, while the actual yield is the quantity or amount that you actually obtain at a particular step.

insert → water activity from p. 110

Proposed § 111.3 defines "you" as "a person who manufactures, packages, or holds dietary ingredients or dietary supplements." "You" is the recommended "plain language" term designed to make regulations easier to understand. In this proposed rule, "you" refers to any person, within the meaning of section 201(e) of the act, who engages in any activity covered by this proposed rule. You should note that "you" includes, but is

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not limited to, the owner of the manufacturing firm as well as supervisors responsible for ensuring that these CGMPs are followed. In other words, "you" can be the person who owns the dietary ingredient or dietary supplement company as well as persons who work for the company.

Proposed § 111.3 defines "water activity" as "a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature." The proposed definition is consistent with the definition at § 110.3(r) and 21 CFR 113.5(w) and 114.5(h). Water activity can play an important role in promoting microbial growth, and that, in turn, can play a part in the contamination of your components, dietary ingredients, and dietary supplements.

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

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

Proposed § 111.5 would require that you comply with the regulations in proposed part 111, and with other applicable statutory provisions, and regulations under the act, related to manufacturing, packaging, or holding dietary ingredients or dietary supplements. Other statutory provisions or regulations that may apply to the manufacture, packaging, or holding of dietary ingredients or dietary supplements include, but are not

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

public health and safety risks may be present. We also invite comment on our legal authority with respect to these issues.

5. Exclusions (Proposed § 111.6)

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

We recognize that including in the proposed rule persons who engage in the activities related to the harvesting, storage, or distribution of such commodities, as described previously, could reduce the risk of microbial contamination in dietary ingredients and dietary supplements. Nevertheless, the proposal does not contain requirements for persons handling such commodities before distribution to a dietary ingredient or dietary supplement manufacturer because the scientific basis for reducing or eliminating pathogens in various settings is evolving. We invite comments on whether we should include provisions in the CGMP

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

We seek comment on whether we should require, in a final rule, that you establish and follow written procedures to ensure that you comply with the requirements of that section. We believe that any such written procedures should describe, in sufficient detail, the measures you take to ensure that no one is a source of microbial or other contamination and the measures you take to ensure that no one contaminates any material, including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. An example of a written procedure would be a procedure for developing and implementing a training program on hygienic practices in the workplace. As stated previously, we invite comment on whether such written procedures should be required in a final rule, and whether there are other procedures, that we should include in a final rule. Insert #4

A comment to the ANPRM stated that any requirements on disease control should be limited to manufacturing, processing, and handling of raw agricultural material and are not appropriate for manufacturing dietary supplements derived from chemicals. The comment stated that chemical processes are carried out in

Page 125 Insert #4:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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procedures or activities, we are stating that compliance with the regulation requires that you adopt, at the minimum, the procedures or activities listed in the regulation. Therefore, when we state "includes, but is not limited to," we mean that the list of procedures or activities following the "includes" statement is a list of requirements.

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

Proposed § 111.12 would establish basic qualification requirements for employees. Proposed § 111.12(a)(1) would require that you have qualified employees to manufacture, package, or hold dietary ingredients or dietary supplements. We are not proposing a general standard for determining how many employees are necessary, but there should be enough to manufacture, package, or hold dietary ingredients or dietary supplements consistent with these proposed CGMPs. A one-person operation is not precluded provided that one person is sufficient to achieve, maintain, and document CGMPs. However, general manufacturing practice suggests the need for a minimum of two persons, the first to perform the work and a second person to check the work performed to ensure that a manufacturing deviation or an unanticipated occurrence is not overlooked. ~~Furthermore, such oversight may be cost effective in preventing product recalls necessary because a deviation or unanticipated occurrence was not detected and reviewed before the product distribution.~~

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C. Physical Plant (Proposed Subpart C)

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

We have not proposed requirements similar to the food CGMP requirements found in § 110.20(a) for keeping the grounds bordering your physical plant in a condition that protects against contamination of components, dietary ingredients, or dietary supplements. Insert # 28 We invite comment on whether such requirements should be included in a final rule. Section § 110.20(a), identifies several methods necessary for adequate ground maintenance, such as:

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

Page 134, Insert #28:
In order to limit the burden to manufacturers, FDA is not proposing such requirements. However,

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

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

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

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

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

Proposed § 111.15(h)(6) would require that you have trash bins that are constructed and maintained in a manner to protect

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~~We invite comment on whether we should require, in a final~~ rule, that you establish and follow written procedures for the maintenance, cleaning, and sanitation of your physical plant that describe, in sufficient detail, the maintenance, cleaning, and sanitation schedules and methods and the equipment and materials to be used. We believe that following written procedures is important because it can help you maintain your physical plant in a clean and sanitary manner. Written procedures, when used, generally have information regarding a schedule, methods, and equipment to be used to control pests. We believe that, because some insects can produce several times during their lifetime, adherence to a written procedure that provides a schedule for applying insecticides in a way that will prevent any initial and subsequent insect infestation would be effective in preventing infestation. Such adherence would likely be a more effective way of controlling pests than attempting to apply insecticides only after you have noticed insects in your physical plant. As another example, written procedures for cleaning your physical plant may specify the use of a particular cleaning compound in a specific strength or concentration; if you do not establish and follow those written procedures, you may use the wrong cleaning compound, use a cleaning compound too strong and create odors that may contaminate or affect your components, dietary ingredients, or dietary supplements, or use a cleaning compound that is too weak and, therefore, ineffective. As stated

~~previously,~~ we invite comment on whether written procedures for maintenance, cleaning, and sanitation should be required in a final rule~~, and whether there are other written procedures, in addition to those mentioned, that we should include in a final rule~~. Insert #5

~~As stated previously,~~ we invite comment on whether documentation at the time of performance of equipment, utensil, and contact surface maintenance, cleaning, and sanitation and keeping such records should be required in a final rule. ~~However, the proposal would require that the batch production record must show the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch.~~ This would give you a record that you would be able to consult if any questions regarding maintenance, cleaning, and sanitation of equipment used in producing the batch arise. Insert #6

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

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

Proposed § 111.20(a) would require any physical plant you use in the manufacturing, packaging, or holding of dietary ingredients or dietary supplements to be suitable in size,

Page 153 Insert #5:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. 9J

Page 153 Insert #6:
We seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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instruments and controls, and whether there are other procedures, that we should consider including in a final rule. Insert #7

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

Insert #30

- The instrument or control calibrated;
- The date of calibration;
- The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy. A certification of accuracy usually accompanies a standard reference material and often is valid for a specific period of time, but the supplier of the reference standard may recertify the standard's accuracy. The recertification typically involves testing by the supplier to verify that the material maintains accuracy as a testing reference. This information also may help you trace the source of a problem, if one arises, in your dietary ingredients or dietary supplements. For example, if consumers report an adverse event with a batch of dietary supplements, records containing a certification of accuracy of the reference standards used and a history of their

Page 177 Insert #7:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

Page 177, Insert # 30:
Proposed §111.25(c) would require that you must establish a written procedure for calibrating instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement and document that the written procedure was followed each time a calibration was performed or that you must document, at the time of performance, that the instrument and control calibration established in accordance with this section was performed. The proposed calibration requirement gives you discretion in deciding whether to establish and follow a written calibration procedure. If you establish a written procedure for calibrating instruments and controls, you must document, at the time of calibration performance, that the written procedure was performed. If you do not establish a written calibration procedure then you must document, at the time of performance, that the calibration established accordance with this section was performed. You must identify the following for calibrating instruments and controls in any written procedure or at the time of performance:

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surface in locations and in a manner that protect them from contamination. This requirement is necessary to ensure that your portable equipment remains clean and sanitized until used; otherwise, if the contact surfaces on the portable equipment or utensils become contaminated, they could lead to adulteration of your dietary ingredients or dietary supplements.

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

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

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- ~~The date and time of each maintenance, cleaning, and sanitizing.~~

~~These procedures may help ensure that certain steps were taken to maintain, clean, and sanitize equipment; show how and when they were done, and show who performed and who supervised these steps.~~ Those procedures may be helpful to inform you that equipment is being maintained, cleaned, and sanitized regularly and as frequently as is necessary based on the actual use, as opposed to the planned use, of the equipment. Insert #8 ~~For example, you may need to clean your equipment more frequently if the actual rate of production using that equipment consistently exceeds the predicted rate of production. As stated earlier, we invite comment on whether written procedures for maintenance, cleaning, and sanitizing equipment, utensils, and contact surfaces and records documenting that the procedures were followed should be included in a final rule, and whether there are procedures, other than those mentioned, that we should include in a final rule.~~

As discussed later, proposed § 111.50(c)(4) would require that you document, in the batch production record, the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used to producing the batch. Records that document the batch or lot number of each batch or lot of dietary ingredients or dietary supplements processed using a particular piece of equipment or a particular utensil between equipment startup and shutdown for maintenance, cleaning, and

Page 184 Insert #8:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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Observations, inspections, and checks of the equipment will help you to determine if critical factors such as revolutions per minute, temperatures, pressures, process times, and automatic documentation are being controlled by the system. Under proposed § 111.30(b), examples of controls to ensure that the equipment functions in accordance with its intended use include:

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

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

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are procedures, other than those mentioned, that we should include in a final rule. Insert #9

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

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

Page 191 Insert #9:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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

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

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under minimal production stress but falter under high stresses of equipment speed, data input overload or frequent or continuous multi-shift use, unexpected sequences or order of events and a harsh environment.

Repeating tests enough times to assure a reasonable measure of consistent reproducible results. In general, at least three consecutive, successful test runs should be made to cover different operating conditions.

Documenting the verification program. Documentation should include a verification protocol and test results that are specific and meaningful in relation to the attribute being tested. For example, if a temperature sensor's reliability is being tested, it would be insufficient to express the results merely as "acceptable," without other qualifying data such as temperatures observed, duration of the test, and the temperature range tested. The individual(s) responsible for conducting, reviewing, and approval of the verification should be identified in the documentation.

Initiating reverification when significant changes are made to the system or when errors are noted. For example, reverification is needed when a major piece of equipment is replaced and when software changes such as

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~~time, temperature, sequence of routine events, data edits, or data handling are made.~~

~~These verification elements differ from the controls that ensure~~ equipment functions in accordance with its intended use as described in proposed § 111.30(b). The controls established under proposed § 111.30(b) would routinely monitor certain equipment operations. Equipment and process verification is primarily performed before first use to support a high degree of confidence that the equipment will consistently perform as it is supposed to and when significant changes are made or when system errors are noted. FDA believes it is important to verify that equipment performs as it should before first use and thereafter as needed. For example, when certain changes are made to the system, verification is necessary for protecting the integrity of ~~the dietary ingredient and dietary supplement manufacturing process~~. Although ~~your~~ verification steps ~~will~~ vary according to the nature of the dietary supplement and the complexity of the process, the basic elements of a verification system would be generally applicable to all dietary ingredients and dietary supplements ~~and~~ provide a foundation for building a comprehensive approach to ensure that the equipment performs in a predetermined way. ~~Verification is relevant to all equipment processes, including but not limited to computerized systems involved in the manufacturing process. (In this instance, the term "verification processes" includes initial verification and reverification.)~~

The primary benefit of a verification system would be to but verification could impose additional costs on manufacturers.

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~~Verification applies to all manufacturing steps in the creation of the finished product, including but not limited to cleaning, weighing, measuring, mixing, blending, compressing, filling,~~ packaging, and labeling.

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

Insert ^ #10

E. Production and Process Controls (Proposed Subpart E)

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

Page 195 Insert #10:
We seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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- 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.

Insert ka from p 220

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. Insert #24

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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. Proposed §111.35(j)(4) would require that for any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, the proposal would require that you reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that inprocess adjustments are possible to correct the deviation or occurrence. You would be able to reprocess a rejected component, dietary ingredient, or dietary supplement if the quality control unit approves such reprocessing. However, the proposal

move to page 219 but between [ ] on pp220-221

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

Page 219, Insert # 24:
The requirements of this section do not mean that the manufacturer needs a large number of employees.

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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

If a test or examination is performed on a production batch, you must record the test or examination result in the batch production record in accordance with § 111.50(c)(10).

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- 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.

insert #25 ✓

Page 226, Insert # 25:
This requirement does not mean that the manufacturer needs a large number of employees.

Food and Drug Administration
Center for Food Safety and Applied Nutrition

Office of Nutritional Products, Labeling, and Dietary Supplements
Division of Standards and Labeling Regulations
Dietary Supplements Team, HFS-821

TO:

Name: Ken Smith

Organization: _____

Phone: _____

Fax Number: 301-827-1696

Number of pages: 31-60 of Corrected proposal page

Date: 1-13-03

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Comments: 2 of 3 for OMB

DS CGMP Proposal

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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

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

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dietary supplement. If your quality control unit makes decisions concerning releasing dietary ingredients and dietary supplements for distribution, it will prevent you from releasing for distribution an adulterated dietary ingredient or dietary supplement before the necessary tests results confirm that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

Your quality control unit must document, at the time of performance, that it performed the review, approval, or rejection requirements established in accordance with proposed § 111.37 by recording the date when the review, approval, or rejection and requirement was performed, 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. Insert 10a ~~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)

Page 232 Insert 10a:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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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). Insert #11 ~~The written procedures that you should consider include those for:~~

- ~~Receipt;~~
- ~~Identification;~~

Page 239 Insert #11:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

- 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

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mechanically into or onto a component, dietary ingredient, dietary supplement, or contact surface or that you use to clean any contact surface must be treated in such a way that the component, dietary ingredient, dietary supplement, or contact surface is not contaminated.

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

(2) You must calibrate before first use; and

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

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

(c) you must (a) ~~The person who performs the~~ instrument and control calibration established in accordance with this section ~~must~~ document at the time of performance that the ~~calibration~~ was performed. ~~The documentation must include, but not be limited to:~~ (d) You must identify the following for calibrating instruments and controls in any written procedure or at the time of performance.

(1) The instrument or control calibrated;

(2) The date of calibration;

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

(4) The calibration method used including appropriate

?) (1) Establish a written procedure for calibrating instruments and controls you use in manufacturing or testing a component, dietary ingredient or dietary supplement and document that the written procedure was followed each time a calibration is performed or

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. Insert #36 Information on packaging and labels materials will also be helpful in case an adverse event occurs; and
- Written instructions including, but not limited to:

Page 247 Insert #36

We are not aware of evidence of that dietary supplement manufacturers are using unlawful containers. Section 201(s) of the ~~Food, Drug and Cosmetic Act~~ defines" food additive" to mean any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in it's becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use). Materials used in packaging that come in contact with food or that react chemically with food, may be considered to be food contact substances or food additives. Foods and dietary ingredients may contain active substances that can react with packaging materials. Thus, FDA is proposing a CGMP requirement that manufacturer's use containers that are lawful under the act and that do not impose a risk such as leakage or the possibility of physical contamination of dietary ingredients or dietary supplements.

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your quality control unit to review them. As stated earlier, consumer complaints related to an illness or injury related to a pharmacologically active substance of a particular dietary ingredient, such as aristolochic acid, would not be a consumer complaint within the meaning of that term in this proposal and thus would not be of the type that the quality control unit must review under this proposed rule.

Proposed § 111.95(b) would require that your quality control unit review all consumer complaints involving the possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any of the other requirements in this part, including those specifications and other requirements that if not met, may results in a possible risk of illness or injury, to determine whether there is a need to investigate the consumer complaint. Insert #28 If the quality control unit determines that an investigation is unnecessary, it would be helpful to you if your quality control unit documents why an investigation was not necessary. This information would be useful to you because it could save time if you receive additional similar consumer complaints about a particular product.

Proposed § 111.95(c) would require that your quality control unit investigate a consumer complaint when there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event. For example, if a manufacturer uses too much of a dietary ingredient in a dietary supplement (e.g., 400 to 4,699 µg of selenium instead of 200 µg of

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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. Insert #26

✓

Page 251, Insert # 26:
and does not mean that the manufacturer needs a large number of employees.

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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~~

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~~there are other procedures that we should include in a final rule.~~ Insert # 12

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.

Page 253 Insert #12:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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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;

including, but not limited to, the person responsible for weighing or measuring each component used in the batch and the person responsible for adding the components to the batch

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- 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

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- 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. Insert #27 FP 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

Page 256, Insert #27:
We seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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

Specifically, proposed § 111.50(d) would require your quality control unit to review, in accordance with § 111.37(b)(5) the batch production record. If a batch production record deviates from the master manufacturing record, including any deviation from specifications, proposed § 111.50(d)(1) would require your quality control unit to conduct a material review and make a disposition decision and record any decision in the batch production record. Proposed § 111.50(d)(2)

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would instruct your quality control unit to not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.

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

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

Proposed § 111.50(f) would prohibit you from reprocessing a batch that deviates from the master manufacturing record unless your quality control unit approves it for reprocessing. Proposed

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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.~~

Insert # 13

Page 273 Insert #13:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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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~~ The person who performs the material review and disposition review required in accordance with this section Would be required to document at the time of performance the results of the material review and disposition decision ~~and such~~ In accordance with §111.50(d), 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~~

45

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~~. Insert #14

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

Page 283 Insert #14:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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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.~~ Insert #15

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,

Page 292 Insert #15:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength and composition of the dietary ingredient or dietary supplement. Further, we seek comment on whether any of the proposed requirements in this section are not necessary to prevent adulteration and to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments assert that certain provisions are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. If comments agree that the proposed requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

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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.~~ Insert #16

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,

P 296 Insert #16:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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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.~~ Insert # 17

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

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

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

Proposed § 111.83(b) would require that you hold such reserve samples of dietary supplements in a manner that protects against contamination and deterioration. Further, this provision would require that you hold the reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use. This proposed requirement also would require that you use the same container-closure system in which the dietary supplement is

Page 297 Insert #17:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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manufacturing. Further, records of any reprocessed batch or batch manufactured using the returned product will be useful in the event that a problem arises with a particular batch that is manufactured with returned product. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures. We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for identifying, quarantining, and salvaging returned dietary ingredients and dietary supplements. ~~In addition, we invite comment on whether there are other procedures that we should include in a final rule.~~ Insert #18

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

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

As discussed previously, proposed part 111 also would apply to foreign firms that manufacture, package, or hold dietary ingredients and dietary supplements that are imported or offered for import into the United States, unless imported for further processing and export under section 801(d)(3) of the act. It also would apply to persons who distribute imported dietary

Page 301 Insert #18:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

- Is not sold or offered for sale in domestic commerce.

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

We invite comment on whether we should require, in a final rule, that you make and keep records on the distribution of dietary ingredients and dietary supplements that you manufacture, package, or hold. ~~We believe that such records may be of benefit to you to facilitate recall actions if you choose to recall a product.~~

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

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

~~Proposed § 111.95(a) would require that you keep a written record of each consumer complaint~~. As stated in § 111.3, consumer complaint refers to a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements of this part, including those that, if not met, may result in a possible risk of illness or injury. Thus, whether the complaint was sent by regular mail, electronic mail, or any other form of

Proposed § 111.95(e) would require that you keep a written record of every consumer complaint that is related to good manufacturing practices.

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written communication, or whether received orally, you would be required to keep a written record of each consumer complaint. You should include all information that would allow your quality control unit to determine whether an investigation of the complaint is necessary.

Proposed § 111.95(a) would require that you have a qualified person review all consumer complaints to determine whether the consumer complaint involves a possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a possible risk of illness or injury. A "qualified person" would be a person who has the training and experience to determine whether a complaint represents a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements in this part, or represents a possible risk of illness or injury that is unrelated to such failure. The qualified person's review is important for distinguishing between those consumer complaints that your quality control unit must review and those consumer complaints that represent a consumer's dissatisfaction with a dietary ingredient or dietary supplement that is unrelated to a possible failure to meet specifications that would be required by this proposal, or any other requirement in this part. For example, some consumer complaints about quality may simply express a personal dislike of the taste, color, odor, or size of tablet, which would probably not require

Page 306, Insert # 28:
When there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event, such as a report of an illness or injury that may be due to a wrong ingredient or wrong label, then the manufacturer would be required to do an investigation that includes batch records associated with the dietary ingredient or dietary supplement involved in the consumer complaint.

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selenium), it is a manufacturing error that may result in an adverse event. Further, if a communication alleges consumer dizziness, vomiting, or lightheadedness after consuming several dietary supplements, it is a adverse event report that is worthy of quality control unit investigation.

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

Proposed § 111.95(f) would require that you make and keep a

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problem applies to more than one product. We suggest that you submit these reports within 15 days after you receive such information to the FDA MedWatch program by calling our "MedWatch" program (our database for reporting possible adverse events) at 1-800-FDA-1088 (1-800-332-1088) to request that a reporting form (one-page, return postage paid) and instructions on how to complete the form be mailed to you, downloading a form and instructions from the MedWatch internet site at www.fda.gov, or using the interactive form available on the MedWatch internet site at www.fda.gov.

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

Proposed § 111.95(f) addresses documentation and recordkeeping. Consumer complaints can alert you (and us) to potential quality problems with a product that is related to good manufacturing practices, such as cases where the manufacturer used the wrong ingredient or put the wrong label on a product. A

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prudent manufacturer, therefore, must investigate any complaints regarding its products because the results of its investigations might lead to solutions or improvements that will make the product or manufacturing process better and benefit the manufacturer and consumers.

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

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

We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for receiving, reviewing, and investigating consumer complaints. ~~We believe that it may be helpful to have such a procedure in place before you get consumer complaints so that you know how to handle such complaints when they arrive. In addition, we invite comment on whether there are other procedures that we should include in a final rule.~~ Insert #19

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

Page 310 Insert #19:
If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

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

Proposed § 111.125(a) would apply to all records covered by the proposed rule and would require that you keep those records for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with those records. Insert #29

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

Proposed § 111.125(c) would require that you make your records available for inspection and copying by us when

Page 311, Insert # 29 :
Retention for 3 years beyond the date of manufacture would be appropriate for follow up of consumer complaints received during the marketing period.

1 word

2000 Ed. GPO Style manual p. 97

Page 324 Econ Insert #31

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

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VII. Analysis of Impacts

A. Introduction

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

Insert #31

The Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 et seq.), requiring cost-benefit and other analyses, in section 1532(a) defines a significant rule as "a Federal mandate that may result in the expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100

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million (adjusted annually for inflation) in any one year." The current inflation-adjusted statutory expenditure is a threshold of $112 million. Since the mean estimated annual expenditure for this proposed rule is below $112 million, FDA has determined that this proposed rule, if it were to become a final rule, would not be a significant rule under the Unfunded Mandates Reform Act of 1995.

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

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

B. Preliminary Regulatory Impact Analysis

1. The Need for the Proposed CGMP Regulations

The proposed CGMP regulations are needed because establishments that manufacture, package, and hold dietary ingredients and dietary supplements may not have sufficient

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to encompass sanitation prerequisites that are met, writing a HACCP plan, and monitoring critical control points. The benefits and costs of the HACCP plan would be generated by controls for a narrower set of hazards in the manufacturing, packaging, and holding processes than those covered by this proposal, and would not include the other benefits and costs generated by the proposed rule especially the reduced consumer search costs, because uniform product quality would not necessarily be assured. Insert #32

e. Require final product testing only. FDA could propose that manufacturers test their finished products for identity, purity, quality, strength, and composition but not include any of the other mandatory provisions of the proposed regulation. The advantage of this option is that it would be the least costly option of those considered. Many firms already test some of their finished products, reducing the impact of this option. Approximately 69 percent of manufacturing plants conduct finished product testing and almost 65 percent of all finished batches in the industry are already tested using physical, chemical, microbiological, visual or organoleptic testing techniques (Ref. E2). The problem with this option is that finished product testing alone cannot ensure product quality for some types of products. Not every finished product currently has a test that confirms identity, purity, quality, strength, or composition,

Page 339, Insert #32:
The advantage of HACCP as an option to prevent product contamination is that it does not specify detailed manufacturing requirements. The disadvantage is that in the absence of uniform controls there would not be uniform minimum product quality across the industry and consumers would not derive the same benefits from lower search costs.

Food and Drug Administration
Center for Food Safety and Applied Nutrition

Office of Nutritional Products, Labeling, and Dietary Supplements
Division of Standards and Labeling Regulations
Dietary Supplements Team, HFS-821

TO:

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Number of pages: 61-78 of Corrected proposal Changes

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Comments: 3 of 3
For OMB
DS CGMP Proposal