II. SECTION BY SECTION COMMENTS

The Preamble

In the preamble to the proposed rule, FDA discusses many of its assumptions and much of its rationale that was considered in developing the proposed rule. Without exhaustively discussing each assumption or rationale of FDA, NNFA discusses below a few issues it believes deserve consideration by FDA in developing a framework for the final rule. The main considerations are: (a) the final rule should be "modeled after" food GMPs in order to comply with DSHEA; (b) existing dietary supplement cGMP programs, such as the NNFA certification program, are well designed and represent useful examples of flexible yet effective GMP programs; and (c) dietary supplements have an admirable safety record.

A. The Final Rule Must Comply With DSHEA

1. Congress Explicitly Required Dietary Supplement cGMPs to be "Modeled After" Food cGMPs

Congress directly and unambiguously required dietary supplement cGMPs to be "modeled after current good manufacturing practice regulations for food." FFD&C Act section 402(g)(2). 21 U.S.C. 342(g)(2). Congress intended dietary supplements cGMPs to be general and flexible in nature (as are food cGMPs), and that FDA include more specific standards only for tests necessary to assure the identity, potency and purity of individual dietary ingredients and dietary supplements.

NNFA is concerned about the extent to which the proposed rule has not been modeled after cGMPs for food, and in some cases even exceeds GMPs for drugs. In the Preamble, FDA supports its position by arguing that: (a) the dictionary meaning of "modeled after" suggests that the rule should be "preliminarily patterned after" food GMP, and (b) because practical similarities exist between dietary supplements and drugs, hybrid food and OTC drug GMP requirements are necessary.

FDA should reconsider how the term "modeled" is used in DSHEA. When defined as a verb, as it is used in DSHEA, "modeled" is intended to require that supplement cGMPs conform to food cGMPs. That is, there should be similarity between dietary supplement and food cGMPs -- such as the general and flexible nature and costs that do not overly burden the industry.

As foods, dietary supplements have always been subject to food cGMPs with apparent congressional blessing as DSHEA mandated that supplements "shall be deemed to be a food with the meaning of [the FFD&C Act.]" FFD&C Act section 201(ff). As such they continue to be regulated under the food cGMPs until FDA exercises the option to impose supplemental standards. Although NNFA fully supports dietary supplement cGMPs, we do not believe Congress would have made the establishment of dietary supplement cGMPs "optional" if it had significant concerns about the propriety of applying the existing food cGMPs to supplements or envisioned a cGMP program that in some respects exceeds the requirements imposed under drug cGMPs.

2. Legal Authority Supports NNFA's Interpretation

DSHEA clearly references the limitation of FDA's discretion regarding dietary supplement GMPs. The U.S. Supreme Court, in Chevron v. Natural Resources Defense Council, 104 S.Ct. 2778, addressed the burden FDA must meet with regard to interpreting these references: "When a court reviews an agency's construction of the statute which it administers, it is confronted with two questions. First, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress. If, however, the court determines Congress has not directly addressed the precise question at issue, the court does not simply impose its own construction on the statute, as would be necessary in the absence of an administrative interpretation. Rather, if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute."

The existence of several definitions that can be attributed to the term "model" does not lead to a determination that the term is ambiguous under Chevron. "Ambiguity is a creature not of definitional possibilities but of statutory context." Brown v. Gardner, 513 U.S. 115, 118, 115 S.Ct. 552, 555. (1994).[1] We believe that the meaning of "model" is clear in context of the entire statute and a by giving a more thorough analysis to the plain meaning of the term than FDA manages and therefore it is not ambiguous.

Although we disagree, if FDA's interpretation of section 402(g)(2) merits deference under Chevron as ambiguous, it is still clear from the arguments above that Congress intended for DSHEA to limit the FDA's discretion to impose overly detailed and costly cGMP standards. In direct contrast, FDA chose a much more expansive interpretation of Congress' mandate. For this reason, FDA's interpretation is not based on a permissible construction of the statute.

3. Other Sources Support This Interpretation

NNFA's interpretation of Congressional intent is supported by other sources. NNFA and its legal counsel took part in drafting DSHEA. FDA's discretion to impose cGMPs was limited because "Congress was mindful of the distrust that had been created between FDA and the supplement industry. Herbal product manufacturers believed that FDA might try to impose standards for quality control testing that could never be met. Other manufacturers feared that drug-styled cGMPs would impose such burdensome costs that small businesses would not be able to operate."[2]

These concerns were reiterated in a December 22, 1997 letter from one of DSHEA's primary sponsors, Orrin G. Hatch, to FDA:

---

[1] As compared with National Railroad Passenger Corporation v. Boston and Maine Corporation, 503 U.S. 407, at 419, 112 S.Ct. 1394, at 1402 (1992), which states: "The existence of alternative dictionary definitions of the word 'required,' each making some sense under the statute, itself *indicates* that the statute is open to interpretation." [Italics added] We note that the court does not state that the presence of multiple dictionary definitions establishes *as a matter of fact* that the term is ambiguous.

[2] Scott Bass, GMPs for Dietary Supplements: Raising the Bar, May/June Food and Drug Law Institute Update (2003), at 4-5.

"As you are perhaps aware, one of the major goals of DSHEA was to rectify the Food and Drug Administration's (FDA) traditional animosity toward supplement products, and the agency's propensity for taking action against supplement products by averring that they were in fact drugs or unapproved food additives. Some of the legal theories the FDA used to make that argument were later held to be invalid in the court system. And so, as the sponsor of DSHEA, it is important to me that the FDA operate within both the letter and the spirit of that law."[3]

B. Existing Dietary Supplement cGMP Programs are Well Designed and Represent Useful Examples of Flexible Yet Effective Programs

The NNFA cGMP program and the NSF/ANSI and USP programs represent effective cGMP standards at work. They were all developed in consultation with a wide variety of experts, including FDA, and have been tested and implemented by many well-known companies. NNFA recommends that FDA include standards from them where suitable in the final rule.

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 directs federal agencies to use voluntary consensus technical standards whenever possible: "[A]ll Federal agencies and departments shall use technical standards that are developed or adopted by voluntary consensus standards bodies, using such technical standards as a means to carry out policy objectives or activities determined by the agencies and departments."[4]

The NNFA cGMP program and the NSF/ANSI and USP standards are all technical standards which provide sound and current practices which help responsible companies develop effective cGMP programs. We believe them to be consistent with the federal law and not impractical for FDA to have utilized more broadly in its cGMP proposal. They represent appropriate and suitable controls, including the use of a certificate of analysis, to assure that safe and accurately labeled dietary supplements are manufactured. They are general in nature and allow companies to comply without extraordinary costs being imposed.

1. NNFA cGMP Certification Program

Since January 1999, NNFA has managed a cGMP program, modeled after the recommended cGMP guidelines which industry submitted to the FDA in 1997, and developed through consultation with member companies, other trade associations and legal counsel. The NNFA program is based upon third-party inspections. Comprehensive audits are conducted of a manufacturer's cGMP program in the areas of personnel, plant and grounds, sanitation, equipment, manufacturing operations, quality control, distribution, and post-distribution practices. Auditors have extensive cGMP and FDA experience in both the food and drug fields.

---

[3] Letter from Orrin G. Hatch, Member of Congress, to Michael A. Friedman, M.D., Lead Deputy Commissioner, Food and Drug Administration (December 22, 1997).

[4] There is an exception to this requirement in Paragraph 3 of this subsection, which states that "if compliance with paragraph (1) of this subsection is inconsistent with applicable law or otherwise impractical, a Federal agency or department may elect to use technical standards that are not developed or adopted by voluntary consensus standards bodies if the head of each such agency or department transmits to the Office of Management and Budget an explanation of the reasons for using such standards...."

To date, over 40 companies have been certified under the program and nearly 60 companies are registered to begin the audit process.

NNFA also requires members who manufacture dietary supplements under their own label to participate in our "TruLabel Program." The backbone of the TruLabel program is random testing of products by independent laboratories against what is claimed on the label to be in the product. We also have coordinated the testing of products for specific contaminants on occasion.

Managing an industry cGMP program and an independent testing program has provided NNFA with insight into how companies of all sizes and resources can achieve compliance with a cGMP program that is general in nature. We have included information on each of these programs in the appendix and have provided suggestions and examples based on our experience.

2. NSF and USP cGMP Programs

Industry and consumer interest in cGMPs has spurred other standard setting groups to also develop cGMP standards. Standards developed by the NSF International and subsequently ratified as industry standards by the American National Standards Institute (ANSI) are based on NNFA cGMPs, along with the advanced notice of proposed rulemaking (ANPR) that FDA published in February 1997, industry input, and input from regulatory agencies such as FDA and consumer groups. NSF/ANSI 173/2003 standards are very similar to the NNFA cGMP standards. NSF's product certification program relies on facility audits to determine compliance with the NSF/ANSI standards and a product testing component.

The U.S. Pharmacopoeia (USP) created its Dietary Supplement Verification Program (DSVP) in 2000. The overall program is product specific and includes a cGMP audit and analytical testing component.

C. Dietary Supplements Have an Admirable Safety Record

In addition to providing undisputed health benefits to millions of Americans, dietary supplements are far safer than most common foods and drugs that consumers use. According to FDA, it received 1,214 reports of adverse events regarding dietary supplements in 2001.[5] Comparatively, FDA received more than 300,000 adverse event reports about drugs.[6] Adverse events related to supplements and reported to FDA in 2001 represent less than half-of-one percent of drug adverse events. Poison Control centers throughout the United States report similar statistics. Reports of adverse reactions to drugs are more than 800 percent higher than dietary supplements.[7]

Although it can be argued that these statistics are a result of consumers' and the medical professions' failure to report supplement adverse reports we believe this is unlikely considering

[5] U.S. Food and Drug Administration, "FDA Proposes Manufacturing and Labeling Standards for all Dietary Supplements," backgrounder, March 7, 2003.
[6] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Financial Management, "Human Drugs," report (2002).
[7] Toby L. Litovitz, et al, "2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System," American Journal of Emergency Medicine, 20, no. 5(2002).

the consistently bad press this industry has received on the subject. More likely, supplement adverse event reporting is low because supplement adverse events are in fact low.

This industry's excellent safety record is germane to the promulgation of supplement cGMPs because FDA's final regulations need to be fashioned in relation to the risk posed by the products being regulated. Here, we believe FDA's proposal exceeds what is required to manufacture safe and accurately labeled dietary supplement ingredients and products.

Subpart A - General Provisions

Section 111.1; Who is subject to these regulations?

- *Foreign Firms*

  FDA is proposing minimum standards necessary to produce safe and accurately labeled dietary supplements for the American consumer. NNFA believes that it is necessary to subject all firms, including foreign facilities that manufacture, package, or hold dietary ingredients or dietary supplements for import to the United States to these standards so that the American consumer is protected.

  Furthermore, since the location of most, if not all, "facilities" should be known as a result of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, we strongly urge FDA to inspect foreign firms actively so as to ensure a level playing field exists between foreign and domestic manufacturers and suppliers. NNFA also urges FDA to extend its existing drug inspection treaties to permit foreign inspections of dietary supplement plants by the host country.

- *Broad Applicability of Dietary Supplement cGMPs*

  FDA clearly intends for this regulation to be broadly applicable. Section 111.2 states "The regulations in this part establish the minimum good manufacturing practices that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement." "You" is defined to mean a person who manufactures, packages, or holds dietary ingredients or dietary supplements. Because the applicability of the proposed rule is broader than some companies in the industry may perceive them to be, the final rule should be abundantly clear about it applicability and provide numerous examples of the types of businesses and practices that are governed under the rule.

  FDA should clarify the border between the exempted production of raw agricultural products and the covered manufacture of raw dietary ingredients. For instance, NNFA believes that under section 111.6 "consolidators" or individuals who purchase raw agricultural commodities for sale to raw ingredient manufacturers will be exempt from the rule, but also could benefit from clarification in the final rule.

- *Applicability of Supplement cGMPs to Raw Dietary Ingredients*

  FDA has proposed production and process controls so distinct from those that exist for similar operations under the food cGMPs that many bulk ingredient manufacturers fear that it may not be feasible for them to continue to participate in the supplement marketplace, which may represent only a small portion of their manufacturing and market, unless they are willing to undertake significant and expensive changes in their manufacturing processes. NNFA does not believe the

solution to this problem is to exempt raw ingredient manufacturers from the rule. Suppliers are key to streamlining the testing scheme and ensuring product quality. NNFA strongly believes that the agency should instead truly "model" their proposal after the food cGMPs and build greater flexibility into the rule so that the gap between food cGMPs and supplement cGMPs is not so great. Companies would then be able to design a program that meets the needs of their specific manufacturing operation.

NNFA conducted a review of FDA's proposed rule with numerous members, including those who supply bulk dietary ingredients for use in dietary supplements. There was a strong consensus that the requirements of this rule would and should apply to raw or bulk dietary ingredients. In addition to the reasons stated in the proposed rule, raw material manufacturers are the only ones with the expertise to evaluate a raw material in some instances, such as with some botanicals and where a unique substance is being marketed.

Manufacturing raw dietary ingredients is different than manufacturing bulk food or drug ingredients. The difficulty to test in-process, or in the finished product, some botanical and other dietary ingredients, makes it necessary to include raw ingredient manufacturers in the rule to ensure consistent high quality from the beginning. It is also appropriate since NNFA, likely others in the industry, will recommend a modified and more flexible testing scheme. Thus, exempting ingredient suppliers from the rule will have a detrimental effect on the goals of ensuring ingredient quality and a streamlined, cost-efficient testing scheme. Accordingly, as FDA is currently proposing, NNFA recommends that the final rule apply to suppliers of bulk dietary ingredients.

Subpart A - General Provisions

Section 111.2; What are these regulations intended to accomplish?

Section 111.2 states that the purpose of these rules is "to establish the minimum current good manufacturing practices that you must use...." The intent expressed in this section is very appropriate considering the variety of ingredients and manufacturing scenarios it will cover. There are several areas, however, where we believe "minimum standards" have been exceeded. We have commented on these areas within FDA's proposal.

Subpart A - General Provisions

Section 111.3; What definitions apply to this part?

- *FDA Definition of "Sanitize"*

FDA proposes that "sanitize" should mean to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the number of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

NNFA recommends that the final rule use the industry standard, as reflected in the food cGMPs[8], the ANPR proposal and NNFA cGMPs, and define "sanitize" to mean:

> to adequately treat ingredient and/or product contact surfaces by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

This requirement is adequate to protect the public health and will require that companies demonstrate their equipment has been sanitized in such a way as to prevent contamination that would alter the identity, purity, quality, strength and composition of the dietary supplement product beyond official or other established requirements. FDA should eliminate reference to a reduction of 5 logs, or a 99.999 percent reduction, as it is ill suited to this industry for the following reasons.

- The Food Code is the wrong model

FDA's argues that dietary supplements, because they are consumed without further processing, are akin to food served in retail outlets, restaurants and nursing homes. Therefore, FDA concludes, supplement manufacturers should meet the "sanitation" requirements specified in the "food code."

We disagree that the food code is a proper model to use in this instance. The Food Code is a multi-use document, designed by experts working to improve food safety at the retail level, to instruct retail outlets such as

[8] 21 CFR 110.3

restaurants and grocery stores and institutions such as nursing homes on how to prevent foodborne illness.

Admittedly, local, state and federal regulators use the FDA Food Code as a model to help develop or update their own food safety rules and to be consistent with national food regulatory policy. That, however, is not the right approach here as those requirements are still intended for use at the retail level.

- Retail and manufacturing operations are distinct

The process of manufacturing supplements shares more in common with food or drug manufacturing. Like dietary supplements, drugs do not undergo significant processing from the manufacturer to the consumer. There are a multitude of manufactured food products that are sold "ready to eat." In both these cases, the existing food or drug cGMP standard for "sanitize," neither of which includes a reference to 5 log reduction, are adequate. Therefore, FDA should allow companies the flexibility necessary to meet sanitation requirements based on individual products and manufacturing operations as is consistent with existing industry practices, food and drug cGMPs.

- Economic cost

With regard to the economic costs, our members interpreted the proposed rule to require companies take the extraordinary and expensive step of shutting down a process line to establish a control measure and then perform challenge testing. NNFA estimates that the cost to comply with this requirement could vary from $50,000 to $200,000 depending on the existing capacity of a company to test for micro-biological contamination. This cost is not justified.

- Contact surfaces

FDA requests comments on whether all contact surfaces should be subject to the sanitation requirements in proposed section 111.3. NNFA strongly urges that they not be. A wide variety of surfaces will be considered contact surfaces under FDA's proposal. However, many contact surfaces, such as those where finished bottles may sit awaiting packaging do not require the same level of sanitation as compared to contact surfaces that come into contact with raw materials since the risk of contamination is lower. Further, by nature, the risk of micro-contamination is not as great for some ingredients. This is an area where FDA should acknowledge there is some variability in the minimum requirements which are needed and allow companies the flexibility to design their operations accordingly.

- *Define the term "identity, purity, quality, strength, and composition"*

  The proposed rule does not define the phrase "identity, purity, quality, strength, and composition," despite using it repeatedly. We urge that the phrase "identity, purity, quality, strength, and composition" be recognized in the final rule to mean:

  > "that the production on a batch-by-batch basis is consistent with the master manufacturing record and is what it is represented on the label to be (identity); is without impurities and is the desired product (purity); is the identity, purity, and strength as established in the master manufacturing record (quality); is the concentration, that is, the amount per unit of use intended (strength); and is the intended mix of product and product-related substances (composition)."

  This is identical to FDA's explanation of the term, with one distinction. Under "quality," the term "for its intended purpose" has been changed to "as established in the master manufacturing record" because quality in the context of cGMPs should be based on the manufacturer's established specifications. This is as opposed to requiring the agency to determine the "intended purpose" of an ingredient or product should it become an issue.

- *Define the term "specification"*

  The proposed rule does not define the term "specification." NNFA recommends that it be defined in the final rule to mean "a defined parameter established for a specific characteristic ensured through visual, chemical or physical testing."

  The establishment of specifications plays a vital role in the framework of controls put into place through cGMPs. Companies are required to establish specifications for the identity, purity quality, strength and composition of incoming and manufactured components, dietary ingredients and dietary supplements. The majority of the testing, quality control unit, laboratory and manufacturing controls required by the proposed rule revolve around specifications. NNFA believes this important term merits a definition.

Subpart B - Personnel

Section 111.12; What personnel qualification requirements apply?

FDA proposes in section 111.12(b) that "Each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties." NNFA recommends that this section be revised to state:

> "Each person engaged in the manufacture of a dietary product should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. Training should be in the particular operations(s) that the employee performs as they relate to the employee's functions. Appropriate documentation of training shall be retained by the manufacturer."

NNFA disagrees with FDA's position that the word "and" includes situations where on-the-job training alone may be adequate and situations where training and experience may be required. Numerous NNFA member companies understandably interpreted the proposed rule to require each person involved in the cGMP process to have both training and experience regardless of those situations where on-the-job training alone may be adequate. If this is not clarified in the final rule, many in the industry fear that FDA inspectors are likely to have a similar interpretation.

Further, FDA invited comments on whether the agency should require companies to document employee training. It is our experience from the NNFA cGMP program that successful quality programs are inextricably connected to appropriate training programs, and that the opposite is also true. Therefore, we believe that written documentation of employee training is an important safeguard to ensuring safe and accurately labeled dietary supplements. It has also been the industry standard for companies to document training, as evidenced in the ANPR, the NNFA cGMPs and the NSF/ANSI 173-2003 standards.

Specifically, NNFA advises companies participating in the NNFA GMP program that initial and periodic refresher training in general GMPs as well as GMPs related to specific jobs/tasks is mandatory for all personnel involved in the manufacture of dietary supplement products. Special sessions are often necessary to address individual department concerns, problem situations, new standard operating procedures and associated forms, and new batch record instructions. Finally, we advise that training programs should be outlined in writing and all GMP training documented and maintained on file.

FDA should redraft section (b) as recommended above by NNFA, as it was proposed by industry in the ANPR, and exists in the food and drug cGMP, so that it is clear within the rule that there are situations where education, training or experience alone will suffice and appropriate documentation must be retained.

- Use of Consultants

  FDA invited comments on whether the final rule should require companies to document each consultant's name, address, and qualifications and include a

description of the services that the consultant provided. Documenting this information, although useful, is not a minimum requirement necessary to ensure safe and accurately labeled supplements, and it should not be mandated by FDA that companies retain it. Documentation in this area should be voluntary.

Subpart B - Personnel

Section 111.13; What supervisor requirements apply?

FDA proposes in section (b) that "[y]ou and the supervisors you use must be qualified by training and experience to supervise." This should be revised to state that:

> "Supervisors must be qualified by education, training and experience (or any combination thereof) to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements in compliance with this rule."

First, as proposed by FDA, the use of "and" alone does not reflect on its face the interpretation FDA has given it on page 12183 of the Federal Register. This term should be changed for the same reasons we stated in section 111.12.

Second, FDA's use of "you and the supervisors you use" is unclear in this context. The term "you" as defined by FDA is quite expansive. In this instance, could the use of "you" be read so broadly as to require the CEO of a company be "qualified" to supervise a cGMP program if those persons actually supervising the program are qualified as such? We think it is arguably so, and therefore this section should be clarified.

Finally, the term "to supervise" is ambiguous. NNFA recommends that the final rule clarify what a supervisor must be qualified to supervise: the manufacture, packaging, or holding of dietary ingredients and dietary supplements in compliance with this rule.

Subpart C - Physical Plant

Section 111.15; What sanitation requirements apply to your physical plant?

- *Cleaning Compounds and Sanitizing Agents*

Section (b)(1) states that:

> "You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use."

NNFA recommends that FDA conclude this section with a reference to ways in which compliance may be verified, as is consistent with food cGMPs. The entire section should be drafted as follows:

> "You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use. Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination."

NNFA has found that manufacturers interpret the proposed rule to require analytical testing of cleaning compounds and sanitizing agents. They are doubtful that an FDA inspector would accept reliance on a supplier's guarantee as adequate to fulfill the mandate of this rule unless it was stated so in the final rule. This is a reasonable assumption considering the heavy reliance FDA has placed on manufacturer conducted testing elsewhere in the proposal.

Further, although a sentence with regard to compliance as verified by a supplier's guarantee or certification appears in the food cGMP; it was eliminated from the proposed supplement rule. This exclusion was notable to a number of our manufacturers since they currently operate under food cGMPs. It reinforced their belief that FDA, at the time of inspection, would not recognize a supplier's guarantee as adequate to meet the rules mandate.

- *Water Quality Requirements Should Apply to Foreign Firms*

FDA asked for comments on the applicability of the water standards to foreign firms. NNFA recommends that FDA not distinguish between domestic and foreign firms with regard to water quality requirements. First, all firms must be able to compete on a "level playing field." More importantly, water quality standards vary from country to country; many countries do not have requirements that are comparable to those in the U.S. and which could result in adulterated

products. The American consumer should be afforded, at a minimum, the protection of U.S. water quality standards.

- *Bathrooms and Hand Washing Facilities*

Companies should be given flexibility, as they are in the food and drug cGMPs, in how they provide employees with adequate, readily accessible bathrooms. Modifying proposed section (g) and eliminating the subsections associated with it would accomplish this:

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

Companies should also be given flexibility, as they are in the food and drug cGMPs, in how they provide adequate hand washing facilities. Proposed section (h) should be modified to read:

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

In both cases, the overall sanitation requirement should control. As long as there is a strong and enforceable standard, companies should have the flexibility to adopt only those measures that are needed to meet the underlying requirement. Finally, both food or drug cGMPs provide companies with needed flexibility; they also use the term "may."

- *Sanitation Supervisors*

Proposed section 111.15(j) states that sanitation supervisors must be qualified by training and experience to develop and supervise sanitation procedures. For the reasons commented on under section 111.12, section 111.15(j) should be revised so that sanitation supervisors must be qualified by education, training and experience (or any combination thereof) to develop and supervise sanitation procedures.

Subpart C - Physical Plant

Section 111.20; What design and construction requirements apply to your physical plant?

Proposed section 111.20(d) requires that any physical plant you use in the manufacture, packaging, or holding or dietary ingredients or dietary supplements must "[b]e designed and constructed in a manner that prevents contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The design and construction must include, but not be limited to:"

NNFA recommends that 111.20(d) be redrafted to state:

> "Be designed and constructed in a manner that prevents contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The design and construction may include as necessary, but is not limited to, the following:"

Companies should have the flexibility to implement only those requirements, whether listed in section 111.20(d) or not, that are necessary to ensure safe, accurately labeled dietary ingredients and dietary supplements. Flexibility is especially critical considering the variety of manufacturing situations that exist for dietary ingredients and dietary supplements. For instance, equipment to control humidity may not be required in some regions, such as in Utah or Southern California. There are also dietary ingredients, such as those in a liquid state where humidity control is irrelevant or that are manufactured in a completely sealed enclosure system where the ceiling surface is not an issue. This rule will be costly enough without mandating that companies be in compliance with requirements that are irrelevant to their operations or unnecessary to achieve the goals of effective GMP.

Subpart D - Equipment and Utensils

Section 111.25; What requirements apply to the equipment and utensils you use?

- *Calibration*

Section 111.25(b), section 111.25(c) and section 111.25(d) put forth detailed requirements for calibrating instruments and controls used to manufacture or test all components, dietary ingredients, or dietary supplements. These sections should be redrafted so that they more closely mirror the more concise requirements in corresponding provisions of the drug cGMPs. NNFA recommends the following:

> (b)(1) You must routinely calibrate instruments and controls that control or monitor critical parameters that you use in manufacturing or testing a component, dietary ingredient, or dietary supplement.
>
> (2) You must establish a written procedure for calibrating instruments and controls that control or monitor critical parameters that you use in manufacturing or testing a component, dietary ingredient, or dietary supplement.
>
> (c) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.
>
> (d) You must maintain written records of calibrations according to Sec. 111.125.

NNFA supports a calibration requirement that is flexible enough to allow manufacturers to draft procedures and make appropriate decisions relative to the calibration of instruments and controls in their operation. We object to the unnecessary level of detail in FDA's proposal. Further, the requirement that manufacturers calibrate instruments and controls "as specified in writing by the manufacturer of the instrument and control" exceeds the drug requirement in that it is more prescriptive. Although this is likely to be a part of the calibration procedure companies should nevertheless have the flexibility necessary to modify their program should the instrument manufacturer's specifications not suit their manufacturing operations.

Further, since we propose that FDA eliminate much of the detail from this section, a requirement that manufacturers have written procedures and keep records of the calibrations will provide FDA with a sufficient means to evaluate the adequacy of a companies program. It will also provide necessary control to meet the underlying intent of the rule, thereby lessening the risk that adulterated products will be produced.

- *Section Number Correction*

  There appears to be two separate paragraphs listed as 111.25(d).

Subpart D - Equipment and Utensils

Section 111.25; What requirements apply to the equipment and utensils you use?

- *Equipment Logs, Procedures and Documentation*

Proposed sections 111.50(c)(3) and (4) will require companies to maintain equipment maintenance, cleaning, and sanitization information within individual batch production records. It would be simpler and more efficient for some companies to maintain equipment logs that can be referenced when necessary. Written procedures in this area are also crucial. NNFA recommends that the following language replace section 111.25(e)(1).

> Procedures must be established and followed for maintenance, cleaning and sanitation of equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients or dietary supplements.

NNFA recommends that the following language be inserted directly thereafter:

> You must document the use, maintenance, cleaning and sanitation of major equipment. Information must be kept in individual equipment logs or batch production records. Documentation must include the date, time, product, and lot number of each batch processed and the cleaning and/or maintenance performed. The person(s) performing the cleaning and maintenance must sign or initial the log to indicate that the work was performed. Entries to the log must be made in chronological order.

NNFA recommends that the following language be substituted in section 111.25(f):

> You must keep documentation as required by this section in accordance with section 111.125.

NNFA's recommendation is based on the belief that companies should have the flexibility to design a program that is suited to their operations. Companies should have the option of using an equipment log as it provides an efficient way to document, trace and review the use, maintenance, cleaning and sanitization of equipment. Since the proposed cGMPs require batch production records to identify all equipment used during production, this will allow for cross-referencing with the equipment log should the need occur.

In contrast, FDA's approach will be awkward for some companies to comply with and does not collect information in a logical order or location where it can be easily referenced and reviewed, such as on the production floor or to provide data

for trend analysis. Although FDA's concern for easing the burden on agency inspectors by requiring all information to be maintained in the batch record is due some consideration, we feel that its benefit is outweighed by the enormous burden on companies to comply with the requirement and the practical difficulties of complying with the proposal. Equipment logs must be referenced in the batch record, and we feel this is sufficient to allow the inspector to request and inspect those documents.

NNFA supports written procedures for the cleaning and maintenance of equipment to ensure consistency in training and compliance. They are currently required in the NNFA cGMP program and we have found them to be an integral part of an effective cGMP framework. In addition, they are effective to ensure that there is consistency in how employees are trained and to assess compliance.

The final rule should not mandate that companies document the maintenance, cleaning and sanitation of utensils. An inflexible documentation requirement here will be labor intensive as a manufacturer might use hundreds of utensils, such as scoops, bowls, trays and screens, during one day of production. We do not believe that contamination from these sources has been a significant enough source of recall in this industry to justify such a requirement.

With regard to contact surfaces, the term is so broadly defined that a documentation requirement would also be unnecessarily labor intensive. In addition, the majority of contact surfaces which pose a risk of contamination would be covered under the log/documentation requirement for equipment that we have proposed above.

Subpart E - Production and Process Controls

Section 111.35(d); What production and process controls must you use?

- *Components*

Section 111.35(d) proposes regulations relative to substances that are likely to become a component or otherwise affect the characteristics of a dietary ingredient or supplement. FDA should eliminate this entire section.

The focus of these cGMPs should be on setting minimum standards for manufacturing systems and steps in the production and distribution of dietary ingredients and dietary supplements which are required to produce safe and accurately labeled products. While knowledge of food additive, color additive and GRAS regulations is certainly advisable, the regulations are at most tangentially related to the manufacturing process. As such, food additive, GRAS or color additive regulations are not specified as production or process controls under the food cGMPs. Drug cGMPs also do not provide for the types of ingredients, or the lawfulness of substances, which may be manufactured as drugs. Supplement cGMPs should more closely follow those models.

Further, it is unnecessary to reiterate regulations that are already established with regard to non-dietary ingredients as this tends to be confusing. Finally, section 111.5 already directs companies to comply with all other applicable statutes and regulations and this is adequate.

- Food additives and GRAS ingredients

The effect of proposed section 111.35(d)(1), (2), and (4) is that any substance, other than a "dietary ingredient," which may affect the characteristics of a dietary ingredient or dietary supplement, regardless of whether the substance becomes a component of the final product, is unlawful unless it is the subject of a food additive regulation, GRAS regulation, or GRAS self-determination. We are apprehensive that FDA is reverting to its traditional food additive theories to regulate supplements. It is unnecessary to open this issue for debate at a time when manufacturers will already be placed under a huge burden to comply with new requirements.

This proposed section also conflicts with DSHEA (which excludes dietary ingredients from the definition of food additive) when the "substance" becomes the dietary ingredient or is undetectable within the manufactured dietary ingredient. For example: A company starts the manufacturing process with an agricultural by-product (soy isolate) that has not been put through any regulatory approval process. Using a chelation process, the company can draw off a natural vitamin E product that has been approved under the food additive provision at a certain point during manufacturing,

and if it continues with a purification process the end product meets the USP monograph for natural vitamin E. This proposed regulation would arguably prohibit this natural vitamin E from being used as a dietary ingredient because the starting material (soy-isolate) was not the subject of a food additive regulation, GRAS regulation or GRAS self-determination. In effect, the dietary ingredient is not exempt from the definition of food additive.

Further, while FDA's proposal seems to mean that the dietary supplement manufactured with the vitamin E produced in the hypothetical above would be adulterated, an identical one, which was manufactured with ingredients "affected" by only approved or GRAS substances, would not be adulterated. The hypothetical ingredient, which meets the USP monograph, could also be used in foods and drugs.

Food additive theories as applied to dietary supplements are a topic which arguably could be resolved in a number of ways. However, unarguably, this section presents complex issues that will only weaken industry's understanding of good manufacturing practices should these requirements become part of the final cGMP regulation. In essence, this is not a GMP topic; it is a topic for another day.

Color additives

Proposed section 111.35(d)(3) mandates that substances used as a color additive must be subject to a color additive listing which includes the use of that additive in a dietary supplement. Currently, none of the listings are specific to dietary supplements. NNFA recommends that this section be eliminated as there is no similar section in the food or drug cGMPs. In the alternative, a color additive listing for "foods generally" should suffice.

FDA provided no rationale in the proposed rule for requiring a categorical listing for supplements. Color additives are not used in any greater amount in supplements than in foods. If anything the amount of color additive consumed in a supplement is probably less because supplements are consumed in smaller amounts than foods and less color additive must be used to achieve the desired effect. Therefore, the potential for any risk is lessened.

Subpart E - Production and Process Controls

Section 111.35(e); What production and process controls must you use?

- *Specification Requirements*

FDA proposes in section 111.35(e) that: "You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration." Specifications must be established for the identity, purity, quality, strength, and composition of raw materials and the final product; in-process controls; and labels and packaging.

NNFA recommends instead that section 111.35(e) be drafted as follows:

> You must establish specifications as appropriate for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. Specifications must be established for:
>
> (i) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;
>
> (ii) Contamination which may lead to adulteration, including, but not limited to filth, insects, or other extraneous material; microorganisms of public health significance; and toxic substances.
>
> (iii) The in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements; and
>
> (iv) The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and
>
> (v) The dietary ingredient or dietary supplement labels and the packaging that may come in contact with dietary ingredients and dietary supplements. The packaging must be safe and suitable for its intended use and comply with all other applicable statutory and regulatory requirements under the Act and must not be reactive or absorptive so as to affect the safety of the dietary ingredient or dietary supplement.

- Specifications for any point, step, or stage

  The opening paragraph of proposed section 111.35(e) provides a gray area that many in the dietary supplement industry fear may be used to require specifications beyond those already required by the master manufacturing record. The master manufacturing record requires that a company "identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration." NNFA is concerned that this proposed section will become a source of confusion. Manufacturers may find themselves arguing about established specifications in a variety of contexts during inspection or other enforcement situations and that FDA may not give due account to manufacturer input with regard to those specifications which are truly critical. For these reasons, NNFA believes that the requirements should mirror proposed section 111.45(a)(1).

- Identity, purity, quality, strength and composition are assured through a system of procedures

  FDA states throughout its proposal and that specifications, procedures and controls must be established to assure the identity, purity, quality, strength and composition of a dietary supplement or dietary ingredient. NNFA believes the term is used too broadly in some sections to require attributes that may not be present at a particular point, step or stage in the manufacturing process. Individual specifications, procedures, or controls may be established to assure only a selection of these attributes at any one time in the production process since cGMPs are a system of procedures and documentation to assure the finished products produced meet all of these requirements. Hence, NNFA has included the qualifier "as appropriate" in our recommendation above.

- Regulatory specifications

  Page 12196 of the preamble proposed rule states that "specifications are regulatory specifications and you would be required to perform testing or examination to confirm such regulatory specifications are met." This is acceptable so long as FDA is flexible during inspections as to what specifications are appropriate. For example, appropriate deference should be due to those the manufacturer has identified in the master manufacturing record and what testing or examination is needed to confirm the specifications are met.

- Filth, insects, and other extraneous material

  Requiring specifications for contamination as a result of filth, insects, or other extraneous material; microorganisms of public health significance; and toxic substances is most appropriate in this section, as opposed to

section 111.35(k). First, the entire section on production and process controls should be simplified, and combining these requirements does that to some extent. Second, it is logical to expect that the requirement to set specifications for extraneous material be listed in conjunction with the other required specifications.

Subpart E - Production and Process Controls

Section 111.35(g); What production and process controls must you use?

- *Testing and Examination*

  Section 111.35(g) states that companies must ensure that the specification established in paragraph (e) are met. It would require companies to accomplish this through finished product testing. In a situation where the quality control unit has determined that there is no scientifically valid analytical method available for such testing, companies must perform testing on each shipment of raw materials and components combined with in-process testing of the same.

  NNFA recommends that section 111.35(g) be revised to read as follows:

  > 111.35(g) You must ensure through appropriate tests and/or examination that each specification that you established under paragraph (e) of this section is met.
  >
  > (1) In lieu of such testing by the manufacturer, a certificate of analysis may be accepted from the supplier of a component or dietary ingredient or dietary supplement, provided that:
  >
  > (a) At least one identity test or examination is conducted on each component, dietary ingredient or dietary supplement. Specific identity tests, if they exist and are generally available, must be used;
  >
  > (b) You establish the reliability of the supplier through appropriate verification of the supplier's test results;
  >
  > (c) The certificate of analysis includes a description of the appropriate test or examination method(s) used, test limits and actual test results data; and
  >
  > (d) You confirm that the supplier is in compliance with 21 CFR Part 111.

- The proposed regulation

  FDA places a great deal of reliance on finished product testing as the primary cGMP control. NNFA believes this is not the best or most appropriate way to assure product safety and quality, is not technically feasible in many instances, and is unduly burdensome economically. Most striking was the cost to test for every component in every batch. FDA's proposal would make it virtually impossible economically for many small

to medium sized companies to produce a dietary supplement with multiple ingredients. These costs are discussed in our economic analysis.

There are also serious technical challenges to industry to test finished product in many instances because of the lack of official or even non-official methods generally available for finished product testing. This issue is discussed at length under section 111.35(h).

FDA's proposal unnecessarily exceeds comparable regulations. For instance, the proposed rule would require that all components, including excipients and processing aids, be tested for conformity to established specification in the finished product on a per batch basis. This exceeds drug cGMP regulations, which require finished product testing for each active ingredient only.[9] Further, the drug cGMP permits the use of a certificate of analysis in lieu of testing all incoming components, including excipients and processing aids, for conformity to specifications.[10] Finally, we note that there is no comparable requirement in the food cGMP to testing each batch when a vitamin or mineral is added to a food product.

- NNFA's recommendation

NNFA recommends that effective process controls, use of verified certificates of analysis and testing, or examination of incoming materials will reduce the likelihood of defects occurring and more predictably result in safe and accurately labeled dietary supplements. As a result, unnecessary finished product testing mandates can be reduced, depending on the ingredient or product being tested, to those tests necessary to assure the identity, potency and purity of individual dietary ingredients and dietary supplements. This more efficient approach to testing will be more effective because the GMP rule will apply to the entire supply chain, and require increased emphasis on in-process controls such as written procedures and documentation in key areas.

* In-process controls

NNFA believes USP guidelines support our recommendation that FDA permit greater reliance in-process controls in recognition that they will provide greater assurances that a batch meets specifications than unnecessary finished product testing. USP states, on page 7 of their 2000 Official Compendia of Standards, that:

> Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test

[9] 21 CFR Part 211.84(d)(2)
[10] 21 CFR Part 211.165(a)

> procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from the batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with Pharmacopeial standards."

In addition to being the current industry standard, as reflected in the USP, NNFA cGMP and NSF cGMP programs and the ANPR, quality programs such as ISO, 6 Sigma and TQM also focus on in-process controls which reduce the likelihood of defects occurring. In particular, ISO, 6 Sigma and TQM attempt to eliminate defects by addressing product conformity to specifications; by maintaining control throughout the production process; and preventing, detecting and dealing with defects at the raw material stage. In the supplement industry, prevention activities include raw material testing, vendor certification, use of standard operating procedures and recordkeeping, process controls, process verification, training, finished product assessment, and on-going internal auditing.

Further, we believe the framework for a reasonable testing program is already in place within FDA's proposal, which requires companies to establish in-process controls, preventive measures, corrective action plans, and written procedures and recordkeeping in some areas. The implementation of these controls renders a great part of the proposed testing scheme unnecessary.

Many of these requirements are also found within HACCP programs where companies are not required to rely so heavily on finished product testing. Systems that involve applying science-based controls, from raw material to finished products, are more effective, according to FDA's backgrounder. As such, "An effective HACCP system requires little end-product testing, since

sufficient validated safeguards are build in early in the process."[11] NNFA believes the same principles should be reflected in the dietary supplement cGMPs and that finished product testing mandates could be eliminated, or reduced depending on the ingredient or product being tested.

* Verified certificates of analysis

It is crucial that FDA permit the use of verified certificates of analysis to show scientifically valid analytical testing has been conducted. Certificates of analysis are a key component of the manufacturing process, they are used by similar industries, and there is no economically feasible alternative. The reliability of certificates should be required to be demonstrated through (a) identity testing, (b) maintenance of documentation of specific and appropriate test results, and (c) appropriate verification of the information provided. Additionally, relying companies should be required to confirm that their suppliers have an adequate cGMP program in place.

A certificate of analysis which is verified and based on appropriate testing is the equivalent of a third party laboratory analysis. FDA officials appeared to acknowledge this in their explanation of the rule during the Oakland public meeting. Officials there agreed that relying on suppliers as if they were contract laboratories was acceptable as long as companies were provided with detailed and complete test results to include in their batch record.

Certificates of analysis are acceptable in other industries. For instance, they are suitable to order the release of a detained active pharmaceutical ingredient,[12] with drug components which are not active ingredients,[13] and in the food cGMPs.[14] Dietary supplements do not pose additional risks beyond these industries that warrant treating this industry different in this regard.

NNFA acknowledges that unscrupulous practices by a few outlier suppliers and manufacturers have presented difficult quality issues. However, rogue behavior by a few is typical of many industries and can be tempered through proper enforcement. NNFA believes it is more reasonable to permit the use of verified certificates of analysis than to impose testing requirements that are unnecessarily burdensome and ill-suited to achieve the desired result and simply cannot be met by many companies.

---

[11] Hazard Analysis and Critical Control Point Principles and Applications Guidelines, FDA, 1997.
[12] 65 FR 75718, at 75719
[13] 21 CFR Part 211.84(d) and 21 CFR Part 211.165(a)
[14] 21 CFR Part 110.80(a)(2)

* NNFA's GMP program allows for the use of a certificate of analysis

In so doing, NNFA advises our members that if a manufacturer/supplier wishes to use a certificate of analysis as the basis for releasing a raw material after having performed appropriate identity testing, then the company must first establish the reliability of the certificate. This is done by performing each test or analysis (or having it done by a qualified outside laboratory) that is on the certificate of analysis which have value to manufacturers according to their written raw material specifications. NNFA recommends that this is done on 3 consecutive lots of raw material, then on a minimum of 1 lot annually thereafter. The confirmed results should be within the values reported on the certificate and reasonably close to the manufacturer's established specifications to be considered acceptable.

* Information that should be included on a certificate of analysis

FDA has inquired as to the type of information which should be included on an acceptable certificate of analysis. NNFA currently stresses the following "areas of importance" to our members. They include items that are part of the raw material specifications for a particular ingredient and could affect product processing, finished product potency, purity and label claim. This may include things such as moisture, sieve analysis, identification, potency, results of tests and analyses against established raw material specifications and specifications of any compendia referenced on the label, etc.

* Testing at appropriate levels of the supply chain

A verified certificate of analysis will place much of the testing responsibility on the raw material supplier or the manufacturer of the finished dosage form since only one company in the chain will have to perform the appropriate testing. Other companies down the supply chain can rely on a verified certificate of analysis. For example, companies that merely bottle and/or label finished dosage forms should be responsible for potency, identity, and purity, but not have to shoulder the majority of laboratory expenditures. This will lower the extraordinary testing costs imposed by FDA's proposal.

To provide an example, NNFA's recommendations regarding how the final rule should allow for a sliding scale of testing obligations

could break down as such for different companies with different roles in the supply chain:

Entity:	Testing Obligation:
Raw Material Supplier	Raw Material Specifications; Contamination which may lead to adulteration
Contract Manufacturer	Identity; In-Process at Critical Points; Contamination which may lead to adulteration; Batch Release Specifications
Bottler/Labeler	As necessary to ensure purity and stability under conditions held
Distributor	As necessary to ensure purity and stability under conditions held

* Additional safeguards

A revised testing approach, like that proposed by NNFA above will be effective as it is backed up by additional safeguards. First, the rule will apply to the entire industry, including raw material suppliers, and thereby provide several layers of assurance that ingredients and products are being handled according to quality standards. Second, written procedures and documentation will be required in key areas. This will provide FDA with an efficient and effective basis to assess a company's compliance with cGMPs. Third, FDA has proposed a framework of in-process controls that are effective to prevent adulterated products. Last, our testing approach does not relieve manufacturers of the requirement to assure that specifications are met, it simply allows flexibility in determining the most appropriate point in the manufacturing cycle to test and eliminates redundant testing requirements.

* Test frequency

NNFA agrees that testing is necessary. NNFA proposes, however, that appropriate tests are those necessary to assure specification for identity, purity, quality, strength and composition are being met. We believe that it is necessary to test for conformity to specification based on a frequency that has been established under a statistically valid method to ensure manufacturing controls are adequate to produce safe and accurately labeled products. Extensive testing of each batch of finished product is not necessary.

* Confirmation of cGMP compliance

It would be economically impossible for many small companies to conduct audits on suppliers to confirm that they are in compliance with cGMPs. NNFA proposes that it is reasonable to allow manufacturers to rely on the results of a reliable third-party audit as adequate to meet the requirement we are proposing. A third-party audit could include a recent audit by a government agency, independent auditing firms, or in connection with a standards program such as NNFA, NSF or USP cGMP programs.

* Identity testing

NNFA advises companies that are certified under the NNFA GMP program to verify the identity of each lot of raw material. An identity test or combination of identity tests should be sufficiently specific to positively identify the raw material and eliminate other materials. In some cases, testing may be a simple a physical or chemical tests or UV/IR scans. In other cases, TLC or other types of chromatography may be required.

Subpart E - Production and Process Controls

Section 111.35(h); What production and process controls must you use?

- *Testing to Meet Specifications*

Proposed section 111.35(h) states that:

> "You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method."

NNFA recommends that FDA revise this section, and combine it with section 111.35(l) to read as follows:

> You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that includes at least one of the following:
>
> (1) Gross organoleptic analysis;
> (2) Microscopic analysis;
> (3) Chemical analysis; or
> (4) Other appropriate test or examination.

- Test Methodology

FDA proposes that industry must use an AOAC, FDA or other official validated method where one exists.[15] We think that approach is problematic. NNFA recommends instead that the final rule give companies the flexibility to adopt the method that is most suitable to the ingredient they are testing and for the specification it has set. This may or may not be the AOAC, FDA or other official method. Companies should be required to ensure through appropriate rationale and data that the test method used is suitable, consistent, accurate, and yields reproducible results.

USP also allows companies some flexibility to use alternative test methods: "Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in the suitability for determining compliance."

NNFA's recommendation is appropriate for several reasons. First, there are instances where the official validated method is not the best option or suitable due to broad test limits, the characteristics of the ingredients, the

[15] Federal Register page 12198

matrix of the finished product, or the laboratory capabilities of the manufacturer. For instance, some botanical products, including many that are the basis of clinical studies, are developed and tested using methods that are not officially validated as defined by FDA.

Second, some official methods that have been developed to test an individual dietary ingredient are not suitable for finished product testing. This can be due to interference from other ingredients, the complexity of the matrix, sample preparation, etc.

Last, the preamble to the proposed rule states that FDA is "not aware of a situation where an appropriate scientifically valid analytical method is not available." However NNFA was unable to find methods available for some non-standardized herbal extracts with non-selective chromatographic fingerprints, and multiple sources of enzymes such as protease from Aspergillus oryzae. In these situations, manufacturers must rely on strategies such as strict cGMP compliance, chain of custody or documentation control. There may be situations where FDA needs to recognize that such controls are appropriate under the rule.

- NNFA GMP Program

NNFA advises companies certified under the NNFA GMP program that it is not always necessary to use compendial analytical methods (i.e. FCC, AOACI, USP/NF) when they are available for a particular ingredient or product. The procedures uses, however, must be reliable and yield accurate, reproducible results. Should a manufacturer choose to use a non-compendial or industry-recognized analytical method or monograph such as the American Herbal Pharmacopeia, it will need to demonstrate the reliability and accuracy of the method.

- TruLabel Testing Example

In 2002, NNFA tested ginkgo biloba leaf extract, in a finished product, for conformity to label claims as part of our TruLabel testing program. The following example demonstrates the challenges that can occur when testing finished products, even when testing a single ingredient product and when there are validated methods available.

Ginkgo flavonglycosides were analyzed in finished product by high-performance liquid chromatography (HPLC) using an ultraviolet (UV) detector. Ginkgo terpene lactones were analyzed by high-pressure liquid chromatography (HPLC) using an evaporated light scattering detector (ELSD). Both tests used a validated modification of the Institute for Nutraceutical Advancement (INA, now the NSF-INA program) method. The INA methods were specifically validated for the raw material.

Due to the complexity of the finished product matrix, the laboratory performing testing for NNFA was required to modify the raw material method and validate it for finished products. The flavonglycosides analyzed were quercetin, kaempferol and isorhamnetin. The terpene lactones analyzed were bilobalide, ginkgolides A, B and C. Finished products were in the form of softgels, vegicaps, liquids, caplets, tablets and capsules.

Beyond the need to modify the method for use with finished products, another technical issue emerged during the testing. Several of the ginkgo samples were in a unique patented form called a ginkgo Phytosome. The Phytosome is a ginkgo/phospholipids complex. Further modifications and validation of the original INA methods was needed to extract the ginkgo and test the active markers in the sample. Additionally, these methods could not be validated for the liquid products; the most we could achieve was a qualitative result representing the presence of the ginkgo biloba.

Subpart E - Production and Process Controls

Section 111.35(i); What production and process controls must you use?

- *Corrective Action Plans*

  FDA proposes in section 111.35(i)(1) that companies must: "Establish corrective action plans for use when an established specification is not met." NNFA recommends that this section direct companies to: "Establish procedures for use when established specifications are not met."

  In general, NNFA supports in-process controls such as the one proposed here; however, we believe that the variability of situations for which supplement manufacturers would have to establish corrective actions plans is too great for this rule to be effective. Especially as compared to the seafood or juice industries where this requirement is already in place, but which the manufacturing processes are more limited in scope. It is adequate to require companies to establish procedures for handling out of specification occurrences and have drafted our recommendation as such.

Subpart E - Production and Process Controls

Section 111.35(k); What production and process controls must you use?

- *Testing for Contaminants*

  Section 111.35(k) requires companies to test or examine components, dietary ingredients, and dietary supplements for contaminants that could adulterate a product. Such contaminants could included filth, insects, or other extraneous material, microorganisms, or other toxic substances. NNFA recommends that this paragraph be incorporated into (e), relating to the establishment of specifications. This would help to simplify and clarify the testing requirements and eliminate some of the redundancy in this section.

Subpart E - Production and Process Controls

Section 111.35(l); What production and process controls must you use?

- *Test Methods*

  Section 111.35(l) lists appropriate testing methods under this section. They include gross organoleptic analysis; microscopic analysis; chemical analysis; or other appropriate tests. NNFA recommends that this paragraph be incorporated into (h), relating to appropriate test methods. This would help to simplify and clarify the testing requirements and eliminate some of the redundancy in this section.

Subpart E - Production and Process Controls

Section 111.35(m); What production and process controls must you use?

- *Recordkeeping*

  Companies must record results of all testing and examinations performed in accordance with section 111.35(m). NNFA recommends that this paragraph be moved to follow the requirements for appropriate test methods, where these requirements are related and probably best understood without intervening information.

Subpart E - Production and Process Controls

Section 111.35(n); What production and process controls must you use?

- *Material Review*

  Section 111.35(n) directs companies to conduct a material review and disposition decision under paragraph (i) of this section. We believe this paragraph restates the requirement in section 111.35(i)(2) and it should be eliminated.

Subpart E - Production and Process Controls

Section 111.35; What production and process controls must you use?

- *Animal-Derived Dietary Ingredients*

  FDA is considering whether to require specific requirements designed to prevent the use of materials derived from certain animals from regions (BSE Countries) identified in 9 CFR section 94.18. As discussed above with regard to section 111.35(d), NNFA does not think that the cGMPs regulations are the appropriate place to embed information or requirements that exist separately and may require updating as the situation changes. Further, the dietary supplement industry is not unique when it comes to BSE issues; efforts to avoid contamination are fairly consistent in other industries. Therefore, NNFA urges FDA not to design specific requirements for the supplement industry and place them within these cGMPs.

Subpart E - Production and Process Controls

Section 111.37; What requirements apply to quality control?

Proposed section 111.37(b) outlines the responsibilities of the quality unit. NNFA recommends modifying paragraph (b)(12) as such:

> Keep reserve samples of each shipment lot of dietary ingredients and dietary supplements and samples of each batch of packaged and labeled dietary ingredient or dietary supplement (in representative packaging if appropriate). Samples must be retained for 3 years from the date of manufacture or one year past the date of expiration or statement of shelf life if an expiration date appears on the product label. Samples may be used in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with the consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. The reserve samples must:

Representative samples are retained primarily to facilitate consumer complaint investigations. We believe that retaining dietary ingredient samples, along with the finished product samples, provides manufacturers with the appropriate materials needed to conduct an investigation should once be necessary.

Retention of in-process samples will provide little or no value to the quality control process and the elimination of this requirement will not harm the overall integrity of the cGMP program. In-process samples typically are collected to monitor specifications such as tablet or capsule size, dissolution or disintegration, moisture content or composition. Deviations are addressed during the production process. Specifications relative to the finished product will be monitored in the finished product samples. Thus in-process samples have little value over an extended period of time.

Additionally, FDA's proposal requires retained samples to include the finished packaging and labeling; hence it is not necessary to require the retention of separate samples of containers, packaging and labels. The proposed cGMPs also cover dietary ingredient manufacturers that typically packages finished product in drums or large bags. Storing retained samples of these items would be particularly problematic, so companies should be allowed to retain "representative packaging" if appropriate.

Subpart E - Production and Process Controls

Section 111.45; What requirements apply to establishing a master manufacturing record?

Proposed section 111.45 establishes requirements relative to master manufacturing records. NNFA has the following recommendations:

- *Labels*

  Proposed section 111.45(b)(7) requires companies to include a description of the packaging and a copy of the label to be used. NNFA recommends that the section be drafted as such: "A description of packaging; and"

  From a practical standpoint, companies often do not have a label available to include in the master manufacturing record. This is particularly so with contract manufacturers. A description of the label to be used in the master manufacturing record and a requirement to attach a copy of the label to batch record will provide the necessary control.

- *Specifications*

  Proposed section 111.45(b)(8)(v) requires companies to establish written instructions relative to "[c]orrective action plans for use when a specification is not met." NNFA recommends that this section be drafted as such: "Procedures for use when specifications are not met." This is consistent with the recommendation under section 111.35(i)(1).

Subpart E - Production and Process Controls

Section 111.50; What requirements apply to establishing a batch production record?

Proposed section 111.50 establishes requirements for the preparation and use of batch production records for dietary ingredients and dietary supplements. NNFA recommends FDA revise portions of this section as follows:

- *Cleaning Logs*

  Paragraph (c)(4) requires companies to include in the batch production record the "date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch." NNFA recommends this be changed as such: "The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, if this information is not maintained in equipment logs." This is consistent with our recommendation in section 111.25.

- *QC Review*

  Paragraph (d)(2) states that:

  > The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.

  NNFA recommends that this section be drafted as such:

  > The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all release specifications.

  NNFA believes that it is important to differentiate between in-process specifications and release specifications. Some in-process deviations and out of specification results may have no negative impact on the identity, purity, quality, strength and composition of the finished product and companies should be given the discretion to make an appropriate disposition decision in that instance.

- *Batch Review Record*

  Paragraph (e)(1) requires the quality control unit to perform a review of receiving records as part of the batch review process. NNFA recommends this paragraph be eliminated.

  This review is redundant since the QC unit is already required to perform a review of the receiving records when the component, dietary ingredient or dietary supplement is received. At that point it will be rejected/approved, and assigned a unique identifier to be recorded in the batch production record and released for

use. The QC unit should only now have to repeat a review of the receiving records as a result of conducting an investigation or a material review, as is the drug requirement. To require otherwise is redundant. It also poses a fairly large burden on the QC unit as this re-review must be performed for each and every batch production record. In our view, the requirement should be completed properly and only once.

- *QC Review of Reprocessed Batches*

For the reasons stated above, paragraph (g) should state:

> Any batch of dietary ingredient or dietary supplement that is reprocessed must meet all release specifications for the batch of dietary ingredient or dietary supplement and be evaluated and approved by the quality control unit before releasing for distribution. The results of the reevaluation by the quality control unit must be documented in the batch production record;

- *Reserve Samples*

Paragraph (h) requires companies to "collect representative reserve samples of each batch of dietary ingredient or dietary supplement and keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine whether, for example, the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, or composition."

NNFA recommends that this paragraph be eliminated as it is an exact duplicate of the requirements in 111.37(b)(11)&(12), where it is more appropriately placed. In the alternative, NNFA recommends that the rule require companies to "keep reserve samples for 3 years from the date of manufacture or 1 year past the date of expiration or shelf life stated on the product label..."

Subpart E - Production and Process Controls

Section 111.60; What requirements apply to laboratory operations?

Proposed section 111.60(b)(1)(iii) restates the sample collection requirements already contained in section 111.37(b)(11)(i) through (iv). They should be eliminated as the requirements are already stated in and more appropriately placed within the quality control function/unit as is consistent with current industry practice.

Subpart E - Production and Process Controls

Section 111.70; What requirements apply to packaging and label operations

Proposed section 111.70(e) requires that companies "must retest or reexamine any repackaged or relabeled dietary ingredients or dietary supplements. They must meet all specifications and the quality control unit must approve or reject their release for distribution."

NNFA recommends the final rule direct companies to "retest or reexamine any repackaged or relabeled dietary ingredients or dietary supplement for conformity to specifications. The quality control unit must approve or reject their release for distribution."

We are concerned that as drafted this paragraph unnecessarily restricts the ability of the quality control unit to make an appropriate disposition decision.

Subpart E – Production and Process Controls

Expiration Dating

FDA has declined to require expiration or shelf life dating on dietary supplement ingredients. NNFA recommends that FDA include the following paragraph, which is based on a requirement from the NNFA GMP program, within the final rule directly following section 111.70(h):

> (i) All products must bear an expiration date or a statement of product shelf life. Expiration dates or a statement of product shelf life must be supported by data to assure that the product meets established specifications throughout the product shelf life. Such data may include, but is not limited to:
>
> (2) A written assessment of stability based at least on testing or examination of the product for compatibility of the ingredients, and based on marketing experience with the product to indicate that there is no degradation of the product; or
>
> (1) Real time studies, accelerated stability studies or data from similar product formulations.
>
> (j) Evaluation of stability shall be based on the same container-closure system in which the product is being marketed.

Consumers are very aware of practices in the food industry, which incorporate expiration, best before and other dates on the product label to indicate freshness. Consumers have come to expect an expiration or best before date on food products. In fact, one of our members has told us that their number one customer/consumer complaint was the absence of expiration dating on products. In the absence of some type of expiration or shelf life dating, consumers cannot really be assured that a product meets full label claim while in the marketplace and that the dietary ingredient will deliver the health benefits desired by the consumer, or promised by the manufacturer.

In the preamble, FDA points out that there are no "current and generally available methods to determine the expiration date of some dietary ingredients, especially botanical dietary ingredients." We agree; however, as is the case with homeopathic drug products,[16] a company should still be able to assure a consumer that what is stated on the label is free from degradation and that it is safe up to a certain point in time. For instance, if a product is labeled to contain an amount of some herbal ingredient, then the product should contain that stated amount, must be free from microbial contamination, and not otherwise disintegrate through the shelf life, or expiration date, printed on the label.

[16] 21 C.F.R. section 211.166

- *NNFA GMP Requirement for Shelf Life/Expiration Dating*

The NNFA GMPs specify that "All products SHALL bear an expiration date or a statement of product shelf life." The shelf life statement or expiration date defines the time within which the finished product should meet its quality specifications, including any potency label claims.

NNFA GMPs do not specify the type of data required or how much data is required to substantiate the shelf life/expiration date included on the product label. We do advise our members, however, that supportive data should be based on measuring or tracking the following items throughout the shelf life of the product: (a) breakdown of loss of dietary ingredients with potency claims; (b) increases in breakdown products; (c) changes in microbial content; and (d) physical characteristics such as loss of solubility or dispersibility. The data from testing and/or examination of the product should be directly related to the company's established specification for the finished products.

We require companies that participate in the NNFA GMP program to have a written rationale for the shelf life date or expiration date established for each product and to define what stability data is required.

Subpart F – Holding and Distributing

Section 111.85; What requirements apply to returned dietary ingredients or dietary supplements?

Section 111.85 proposes requirements which apply to returned dietary ingredients or dietary supplements. NNFA recommends that this section be revised as follows:

> (a) You must identify and quarantine returned dietary ingredients or dietary supplements.
>
> (b) If the conditions under which returned dietary ingredient or dietary supplement have been held, stored, or shipped before or during their return, or if the condition of the product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the identity, purity, quality, strength or composition of the dietary ingredient or dietary supplement then it shall be handled in accordance with the requirement of section 111.85(c) unless examination, testing or investigations prove the product meets all specifications for identity, purity, quality, strength and composition.

In general, the restrictions placed on companies by this proposed section are excessive and unclear, especially when contrasted with the drug GMP and ANPR requirements. For instance, as proposed, paragraph (b) states that returned product cannot be salvaged if it does not meet specifications; however, paragraph (c) directs the quality control unit to conduct a material review and make a disposition decision to allow reprocessing.

It is common industry practice to accept returns from customers for a variety or reasons (i.e. an incorrect order is shipped, excess inventory, delivery refusal). The majority of returned product can be quickly examined. We think it is unnecessary to conduct testing for all specifications for every returned product. The drug standard is more appropriate; testing should only need to be conducted when some doubt has been cast upon the identity, purity, quality, strength or composition of the product, or if the product was returned for some other GMP-related problem.

Subpart G – Consumer Complaints

Section 111.95; What requirements apply to consumer complaints?

Proposed section 111.95 describes requirements for a company to review consumer complaints, but does not require written procedures be established. NNFA recommends that the final rule require written procedures in this area by inserting the following before paragraph (a), and renumbering the trailing paragraphs accordingly:

> Written procedures describing the handling of all written and oral consumer complaints related to this section shall be established and followed.

Written procedures will encourage companies to handle consumer complaints in a uniform manner and will provide FDA and other auditors with a basis to assess the process being used.

Subpart H - Records and Recordkeeping

Section 111.125; What requirements apply to recordkeeping?

Proposed section 111.125 requires companies to keep written records for 3 years beyond the date of manufacture of the last batch associated with the record. NNFA recommends that FDA modify this section so that companies are given the option of retaining records for 1 year beyond the expiration date on the product should the product contain an expiration date.

NNFA recommends the following language for the final rule, section 111.125(a):

> You must keep written records required by this part for 3 years beyond the date of manufacture, or 1 year past the date of expiration or shelf life stated on the product label, of the last batch of dietary ingredients or dietary supplements associated with those records.