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Comments Regarding the Food and Drag Administration's Proposed Rule

On

Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule;68 Fed. Reg. 12158 (Proposed March 13, 2003)

Docket No. 96N-0417

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Submitted by: Edward Fredericks

96N-0417

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I. Introduction and Summary

Who we are:

Arizona Nutritional Supplements, Inc. (ANS) is a contract manufacturer, specializing in tablet, capsule and powder formulations. We offer full turnkey packaging and distribution services, and maintain a fully operational in-house lab and quality control staff to ensure the quality of our products. Operating in the State of Arizona, we employ nearly one hundred full time employees and manufacture hundreds of unique dietary supplements for many different segments of the industry.

ANS was among the first companies to become certified cGMP through the National Nutritional Foods Association (NNFA) program and we were the first company to become certified by National Sanitary Foundation (NSF) as cGMP. Through our company's own operating procedures, we continue to constantly look for ways to improve the quality of our products and business and have supported the push to have mandatory minimum standards in place in our industry.

Since the announcement of the FDA GMPs, members of our company have taken part in industry workgroups, teleconferences and open forums with the FDA, so that we would be able to take part in the shaping of our industry's future. The majority of our comments are the result of months of meetings with the NNFA and various members of our industry.

Main Issues with the FDA GMPs

➢ Lack of Flexibility creates unnecessary burdens

The lack of flexibility in the proposed rules oversteps the purpose of establishing "minimum standards." The proposed GMPs are written more like a guidance document in comparison to the established Food and Drug GMPs. Requiring our industry to be responsible for the products it manufactures and have quality control parameters is long overdue and welcomed by those of us who have been striving for excellence in quality

manufacturing. However, it is quite detrimental to attempt to write law as a "How To" and/or guidance document . We believe that manufactures should be responsible for maintaining quality standards, but should be allowed the flexibility to enact quality control methods in various manners. By attempting to propose what seems like more of a 'guidance document' as law, it does not necessarily achieve the end result of ensuring the finished product meets its proper specifications; but rather, it attempts to purely homogenize the industry, and in turn, suppress innovation in operating procedures which yield excellent results in safety and quality.

Many of the requests within the proposed rules require duplicate and even triplicate of documented information with a under estimating of the resulting impact. Required testing for each and every ingredient is incredibly impractical in many instances given the unreliability of testing certain ingredients within complex matrixes, not to mention the cost to even attempt this when added to the fact that material will be tested previously, either at a raw material supplier, third-party lab or in-house upon receipt at the place of manufacturing. Unfortunately, the main opportunity presented by the FDA is the presentation of alternate GMP models used which in many cases cannot be presented without sacrificing proprietary business models that have been established over the course of many years of dedication. The public nature of these comments prohibits these from being presented in a confidential manner.

- **Departure from DSHEA**

DSHEA mandated that the FDA GMPs be "modeled after" the Food GMPs. In fact, at many times the proposed rules are stricter then what is required in both the Food and Drug GMPs.

The FDA explanation within the preamble to the rules is that they have taken "modeled after" to mean "preliminarily patterned after." This has led to the attempt in these rulings to provide a hybridized GMP that is more strict and cost prohibitive then the GMPs that have been established for the Drug industry. Not only have definitions been more restrictive (such as the definition for "sanitize" and the attempts to rewrite the definition of dietary ingredients which have already been defined in previous documents) but the requirements are less flexible and more restrictive (such as the requirements for testing each ingredient in every batch of finished products).

This was clearly not the intention of the DSHEA mandate and we hope that after this comment period the FDA takes a step back on the proposed rulings in order to maintain the needed flexibility needed in the final ruling in order to follow the spirit of DSHEA and provide a fair and reasonable code of law for the supplement industry, modeled after Food GMPs.

➢ The perceived costs and benefits are questionable

Our analysis of implementing the GMPs as currently proposed is dramatically higher then what has been proposed by the FDA. Our findings matched many others in the industry as well as results displayed in a survey that the NNFA has included in their own official comments.

In public meetings, the FDA has given large figures to which the attribute future savings to consumers (many of them theoretically calculated from them saving time looking for quality products) without the realization that most consumers will not be able to afford these products any longer. With the inflexible product testing requirements as proposed, costs will skyrocket for products that should be available to consumers for modest prices.

We hope that the FDA can find that quality manufacturing need not be as inflexible and overly burdensome as proposed so that both manufacturers and consumers alike can both win in a marketplace containing both quality AND affordability.

II. Section by Section Comments

Subpart A - General Provisions

Section 111.2; What are these regulations intended to accomplish?

§111.2 states that the purpose of these rules is "to establish the minimum current good manufacturing practices that you must use to the extent that you manufacture, package or hold a dietary ingredient or dietary supplement"

FDA should clarify the types of business for which these rules are applicable. The current level of detail and inflexibility in the document does not account for the variance in manufacturing needs within the entire industry. The necessary operating procedures for companies preparing and producing herbal extracts and vitamins (as a raw material) will be much different from a manufacturer who is manufacturing those finished goods into a solid dosage form (tablet, capsule, etc.). The lack of clarification and the broadness in which this implies necessitates greater flexibility in what manufacturing practices are mandated as law.

Furthermore, it is our strong belief that what follows in this document is much more then the "minimum current good manufacturing practices." There is very little use of the words "adequate" or "acceptable" throughout the entire document, allowing very little room for different methods of quality assurance and control. "Both the food cGMP and the ANPR define "adequate" to mean "that which is needed to accomplish the intended purpose in keeping with good public health practice." This has been used in the food, drug, NNFA and ANPR GMPs and should be allowed to be used in this document to allow for flexibility.

This problem of inflexibility is compounded by the fact that all comments submitted to FDA regarding this docket are public record, therefore disallowing companies to submit standard operating procedures that would show excellent quality results without releasing proprietary business models. Thus, those companies who have developed quality procedures through "Good Manufacturing Practices" will be punished for their development of their proprietary operating models by being forced to follow a carbon copy rule-set which allows for very little innovation and flexibility.

Subpart A - **General Provisions**

Section 111.3; What definitions apply to this part? [1]

➢ **Definition of "Sanitize"**

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

ANS recommends that FDA should use the the definition reflected in the food GMPs, the ANPR proposal and NNFA GMPs, to define "sanitize" in the final rule:

> "means 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 so long as companies can 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 they are 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,

[1] This section is taken in part from comments submitted from the NNFA official comments for Docket No. 96N-0417

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 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. 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 GMP standard for "sanitize", which does not include a reference to 5 log reduction, is 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 GMPs.

✓ Economic cost

With regard to the economic costs, our members interpreted the regulation as drafted to require companies take the extraordinary and expensive step of shutting down a process line to establish a control measure and then do challenge testing. One of the members in our workgroup, a company with a single process line, estimated yearly compliance costs could be as high as $50,000. This cost is not justified.

✓ Contact Surfaces

FDA requests comments on whether all contact surfaces should be subject to proposed sec. 111.3 "sanitize." We strongly urge that they not be. A wide variety of surfaces will be considered contact surfaces under FDA's proposal. However, many of those 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. 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.

- **Definition of "Identity, purity, quality, strength, and composition"**

ANS believes that the lack of a definition of this phrase is problematic considering how often it is used in this document as the guideline for what is to be maintained in every part of the manufacturing process.

ANS proposes (in conjunction with the NNFA) that the phrase "Identity, purity, quality, strength, and composition" is defined 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)."

The distinction made in the above definition is made purposefully with regard to "quality," in order that it is determined by compliance of the manufacturer's established specifications rather then by the agency's determination the "intended purpose" of a particular product or ingredient.

Subpart B - Personnel

Section 111.10; What microbial contamination and hygiene requirements apply?

§111.10(a) states that:

> "*Microbial contamination.* You must take measures to exclude from any operations any person who might be a source of microbial contamination of any material including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredients or a dietary supplement. Such measures include, but are not limited to, the following:
> (1) Excluding any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion, or any other abnormal source of microbial contamination, which may be expected to result in microbial contamination of components, dietary ingredients, dietary supplements, or contact surfaces, from working in any operations until the conditions is corrected; and"

ANS recommends that this passage be rewritten so that it is clearly applicable only for areas of the operation in which contamination of product(s) might occur. Employees that have no contact with the manufacturing areas should not be unable to work areas outside of manufacturing if they are deemed fit to do so.

Subpart B - Personnel

Section 111.12; What personnel qualification requirements apply?

FDA proposes in §111.12(b) that "Each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties."

> "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"

We feel it that by rewording that section, employers are given the flexibility to determine better who they feel is appropriate for a particular position and will give more opportunities for hiring people from different backgrounds in the current job market.

Section 111.13; What supervisor requirements apply?

As in the previous section 111.12, ANS proposes that in each of these sections, the qualifier should be changed to reflect that supervisors can have a combination education, training and experience, as the employer sees fit for the assigned functions.

Second, FDA's use of "you and the supervisors you use" should be clarified in this context. Does the term encompass the owner or CEO of a company to be qualified in the same manner that the supervisor of a Quality Control program? We feel that the multitude of supervisory functions require a flexible definition so that it may reasonably accommodate the many aspects of the industry.

Subpart C - Physical Plant

Section 111.15; What sanitation requirements apply to your physical plant?[2]

➢ Cleaning compounds and sanitizing agents

FDA proposes in §(b)(1) 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."

We recommend that FDA conclude this section with a reference to ways in which compliance may be verified as is consistent with food GMPs. The entire section should be drafted as such:

> "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."

A workgroup that ANS and a number of other companies took part in initially interpreted the proposed rule to require analytical testing of cleaning compounds and sanitizing agents. They were dubious 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, a sentence with regard to compliance as verified by a supplier's guarantee or certification appears in the food GMP; however, the sentence was eliminated from the supplement proposal. This exclusion was notable to a number of our manufacturers since they currently operate under food GMPs. It reinforced their belief that FDA would not recognize a supplier's guarantee as adequate to meet the rules mandate.

[2] Comments for this section were taken in full from the NNFA official comments for Docket No. 96N-0417

➢ Water Supply

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

We recommend that this §111.15(d)(2) be eliminated as it is unnecessary to state this requirement. If water is used in processing or at critical points in the cleaning process, then specifications for its appropriate use will need to be established. Therefore, FDA's ability to enforce the rule is sufficient to ensure safe and accurately labeled supplements without subjecting to inspection, in this instance, documentation that a company may keep to ensure compliance with the rule. We also note that neither the food or drug GMPs explicitly include a documentation requirement in the regulations.

Further, water quality in a community is typically well known because of the public notification requirements which the Environmental Protection Agency (EPA) has established and other resources. Municipal water supplies are also well controlled as a result of EPA regulations. If water quality in a community or country is suspect, FDA can move aggressively to enforce the standards proposed as §111.15(d)(1) and (2), which we wholeheartedly support. Overall, the burden on FDA to enforce as such would be less than requiring every company in the industry to maintain and produce for inspection purposes documentation related to water quality.

➢ Water Quality Requirements Should Apply to Foreign Firms

FDA asked for comments on the applicability of the water standards to foreign firms. ANS 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 GMPs, in how they provide employees with adequate, readily accessible

bathrooms. Substituting the word "may" in section (g) would accomplish this:

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

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

> "(h) 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 FDA has a strong and enforceable standard, needed flexibility within the rule should be clearly granted so that companies have the discretion to adopt only those measures that are needed to meet the underlying requirement. Finally, both food and drug GMPs provide companies with needed flexibility; they also use the term "may."

➢ Sanitation supervisors

FDA states in 111.15(j) 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 changed so that sanitation supervisors must be qualified by education, training and experience (or any combination thereof) to develop and supervise sanitation procedures.

➢ Written procedures for maintenance, cleaning and sanitation of the physical plant

It is unnecessary for FDA to require written procedures for maintenance, cleaning and sanitation of the physical plant. Mandating that a manufacturer must have written procedures will not directly prevent contamination or ensure the identity, purity, quality, strength, and composition of the dietary

ingredient or dietary supplement if a manufacturer is, bottom line, maintaining the physical plant in a clean and sanitary condition. Further ANS does support a requirement for written procedures and documentation relative to major equipment, including those contact surfaces which we think will have a much more significant impact on product quality.

So long as FDA has the ability to inspect and enforce the maintenance, cleaning and sanitation requirements of section 111.15 manufacturers should have the ability to design procedures to satisfy the rule. Adoption of written procedures is highly advisable, but should be voluntary.

Subpart C - Physical Plant

Section 111.20; What design and construction requirements apply to your physical plant?[3]

Proposed §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:"

We recommend that (d) be redrafted as such: "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, but is not limited to:"

Companies should have the flexibility to implement only those requirements listed in §111.20(d) that are necessary to ensure safe, accurately labeled dietary ingredients and dietary supplements. Flexibility is especially critical considering the variety of manufacturing scenarios that exist. 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.

[3] Comments for these sections were taken in part from the NNFA official comments for Docket No. 96N-0417

Subpart D - Equipment and Utensils

Section 111.25; What requirements apply to the equipment and utensils you use?[4]

Calibration

§111.25(b), §111.25(c) and §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 the drug GMPs. We recommend the following:

> (b)(1) You must routinely calibrate instruments and controls with 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 with critical parameters that you use in manufacturing or testing a component, dietary ingredient, or dietary supplement.
> (3) You must maintain written records of calibrations according to Sec. 111.125.
> (d) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

ANS objects to the level of detail in these sections as it is unnecessary. 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.

ANS 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. 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.

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[4] Comments for this section were taken in part from the NNFA official comments for Docket No. 96N-0417

Subpart D - Equipment and Utensils

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

Equipment logs, procedures and documentation

As currently proposed, §111.50(c)(3) and (4) will require companies to maintain equipment maintenance, cleaning, and sanitization information within individual batch production records.

ANS does not argue with the need to keep logs on maintenance and sanitation; however, we feel that it is overly burdensome to require companies to keep multiple instances of these logs within each batch report.

This information can be easily referenced from the batch records so that it can be traced and accounted for without having to be duplicated in multiple documents. This is seen in many facets of the FDA proposed rules, where there it is expected for the manufacturer to include with a batch record, information which can be cross referenced.

A single machine may produce hundreds of batches in a given period of time; we can see no benefit to including that equipment's maintenance record in hundreds of individual batch records. Likewise, a single lot of raw material may be used in hundreds of batches; test results taken upon receipt of this raw material need not be included in each batch file when it is kept on record and can be easily cross referenced and traced through each batch.

Subpart D - Equipment and Utensils

Section 111.30; What requirements apply to automatic, mechanical, or electronic equipment?

§111.30 establishes requirements for automatic, mechanical, or electronic equipment. §111.30(b) relates to calibration. ANS recommends that this section be modified as such: (b) For any automatic, mechanical, or electronic equipment you use with critical parameters and which impact the identity, purity, quality, strength, or composition of a dietary ingredient or dietary supplement, you must:"

This section needs to clearly define its intention as solely for those parts of manufacturing for which the product specifications can be affected. The requirements for a thermostat that is in a sales office should not be as strict as those for a scale for which the quality assurance unit measures tablets.

Subpart E - Production and Process Controls

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

Components[5]

§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. We ask that this entire section be eliminated.

The focus of these GMPs should be on manufacturing steps in the production and distribution of dietary ingredients and dietary supplements which are minimally required to produce safe and accurately labeled products. While knowledge of food additive, color additive and GRAS regulations is certainly advisable, the regulations are 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 GMPs. Drug GMPs also do not provide for these types of ingredients, or the lawfulness of substances, which may be manufactured as drugs. Supplement GMPs should more closely follow those models.

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

I. Food Additives and GRAS ingredients

The effect of proposed §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 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.

We also think there is a conflict with DSHEA, which excluded dietary ingredients from the definition of food additive, when the "substance" becomes the dietary ingredient or is undetectable within the manufactured dietary ingredient. Consider this scenario: A company starts the manufacturing process with an agricultural by-product (soy isolate) that has

[5] Comments for this section were taken in full from the NNFA official comments for Docket No. 96N-0417

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. This is likely one of the consequences Congress was trying to avoid when they stated that dietary ingredients were exempt from the definition of food additive.

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. This is a topic for another day.

II. Color Additives

§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; however color additives are being used in the industry. We recommend that this section be eliminated as there is no similar section in the food or drug GMPs. In the alternative, we think a color additive listing for "foods generally" should suffice.

FDA provided no rationale in their rule for requiring a categorical listing for supplements. Color additives are not used in any greater concentration 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 would seem to be lessened.

Subpart E - Production and Process Controls

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

Specification Requirements[6]

FDA proposes in §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." Specifically, specifications must be established for the identity, purity, quality, strength, and composition or raw materials and the final product; in-process controls; and labels and packaging.

We recommend that §111.35(e) be drafted instead as such:

You must establish specifications as appropriate for points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. Specifications must be established for:
(1) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;
(2) 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.
(3) 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
(4) The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and
(5) 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.

[6] Comments for this section were taken in part from the NNFA official comments for Docket No. 96N-0417

I. Specification for any point, step, or stage

The opening paragraph of proposed §111.35(e) provides gray area for FDA to require specifications beyond those already called for in the master manufacturing record, which requires that a company "identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration." ANS is concerned that we will find themselves arguing about established specifications in a variety of contexts during an inspection or enforcement scenario and that FDA will not give due account to manufacturer input with regard to those specifications which are truly critical. For that reason, we believe that the requirement should be identical to §111.45(a)(1).

II. 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. ANS believes the term is used to require attributes that may not be present at a particular point, step or stage in the manufacturing process. It is likely that 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 GMPs are a *system* of procedures and documentation to assure the final products produced meet all of these requirements. Hence, ANS agrees to include the qualifier "as appropriate" in our recommendation above.

III. Regulatory specifications

FDA states on page 12196 of the preamble 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 FDA is flexible during inspections as to what specifications are appropriate (i.e. giving appropriate deference to those the manufacturer has identified) and what testing or examination is needed to confirm the specifications are met.

IV. 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 §111.35(k). First, the entire section on production and process controls

needs simplifying, and combining these requirements does that so 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[7]

§111.35(g) states that companies must ensure that the specification established in paragraph (e) are met. They are to do 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.

FDA should eliminate the entire section 111.35(g); it should 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 supplement, provided that:
> (a) At least one specific identity test is conducted on such components, dietary ingredient or dietary supplement; and
> (b) You initially establish the reliability of the supplier through appropriate confirmation of the supplier's test results; and
> (c) You confirm the supplier's test results at appropriate intervals, but not less than once every 2 years; and
> (d) The certificate of analysis includes a description of the test or examination method used, test limits and actual test results data; and
> (e) You confirm through inspection that the supplier is in compliance with 21 CFR Part 111. You may rely on a finding of GMP compliance by a qualified standards body to meet this requirement.

[7] Comments for this section were taken in part from the NNFA official comments for Docket No. 96N-0417

I. Mandated final product testing

Using finished product testing as the primary GMP control is not the best or most appropriate way to assure product safety and quality, is not technically feasible in many instances, and is economically burdensome.

USP clearly recognizes the role of finished product testing. They state, 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 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."

It is vital that FDA allow for the use Certificates of Analysis to show scientifically valid analytical testing has been conducted. The reliability of the certificate should be demonstrated through identity testing, and initial plus on-going confirmation of the information provided. Additionally, companies should be required to confirm that their suppliers have an adequate GMPs program in place.

Certificates of Analysis are acceptable in other industries. For instance, they are suitable to order the release of a detained active pharmaceutical ingredient, for human cellular and tissue-based products, with drug excipients, and in the food GMPs.

II. Prevention is the better strategy

Testing finished product may find defects that already exist, but prevention can eliminate them from happening in the first place. This more effective approach, used by quality programs such as ISO, 6 Sigma and TQM, is to focus on defect prevention versus searching for defects in the final product. ISO, Sigma 6 and TQM address product conformity to specifications; maintaining control throughout the production process; and prevention, detection and dealing with defects at the raw material stage. .

The most effect method to assure product safety and quality is to design processes that reduce the likelihood of defects occurring in the first place and then to continually monitor these processes to ensure their ongoing effectiveness. This approach is especially important in this industry as it is not possible to achieve 100% success with finished product testing using our current technical capabilities.

In the supplement industry, prevention activities include raw material testing, vendor certification, use of standard operating procedures and recordkeeping, process controls, process verification, personnel training, finished product assessment, and on-going internal auditing.

III. FDA's proposal is economically impossible

It would be virtually impossible economically for many companies to test every ingredient in a 30- or 40- ingredient dietary supplement, as FDA has proposed would need to be done. We have elaborated on these costs in our economic analysis of this rule.

IV. FDA's proposal is in excess of comparable regulations

All components are required to be tested on a per batch basis under FDA's proposal. This exceeds the drug requirement which allows for a certificate of analysis to be accepted in lieu of such testing. Further, we note that there is no comparable requirement to testing each batch in the food GMP when a vitamin or mineral is added to a food product.

Subpart E - Production and Process Controls

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

Testing to Meet Specifications[8]

FDA proposes in §111.35(h) 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."

We recommend that FDA redraft this section, and combine it with §111.35(l):

> 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.

The decision as to what is the appropriate test or examination is should be based on manufacturer established specifications. ANS objects to a requirement that industry must use an AOAC, FDA or other official validated method where one exists[9] as we think this approach is problematic.

FDA states that they "are not aware of a situation where an appropriate scientifically valid analytical method is not available," however our industry trade association, NNFA, was unable to find such methods available for some glandular materials such as spleen powder and pancreas gland powder, 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 GMP compliance, chain of custody or documentation control. There may be situations where FDA needs to recognize these as appropriate under the rule.

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[8] Comments are taken in part from the NNFA official comments for Docket No. 96N-0417

[9] Federal Register page 12198

There are also ingredients where official analytical methods will likely prove difficult to establish. For instance, St. John's Wort has proven challenging to identify and characterize through the use of markers. In fact, three separate markers for St. John's Wort, each replacing what had been previously thought to be the most important characteristic, have been used in the past 10 years.

Further, there are instances where the official validated method is not the best option due to broad test limits, the characteristics of the ingredients, the matrix of the finished product, or the laboratory capabilities of the manufacturer. It is more reasonable to require companies to show through appropriate rationale and data that the test method used is suitable, consistent, accurate, and yields reproducible results.

Subpart E - Production and Process Controls

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

Corrective Action Plans[10]

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

For custom manufacturers, the amount of specifications can be infinite. We produce many hundreds of batches on a monthly basis, of which there are multiple specifications per batch. As we are acquiring new customers and new formulas are developed, these numbers continue to increase dramatically over time. It is overly burdensome to write a corrective action for each individual ingredient specification but rather reasonable to have written procedures in general for when specifications on a product are not met.

Deviations

§111.35(i)(4) and (i)(4)(i) state 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 you must reject a component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in process adjustments are possible to correct the deviation or occurrence." We recommend that these sections be eliminated as these principles are very well covered in (i)(2) and (i)(3).

Companies should also have the ability to approve and release a batch of dietary ingredient or dietary supplement if an investigation or material review has been conducted and the product has been found acceptable by the quality control unit, although the product may in fact be out of specification. For example, a company has an in-process specification for tablets to have a hardness of 5 to 10 kg but finds that a batch includes some tablets with a harness of between 10 and 13 kg. An investigation reveals that the reason for the outliers was a defective hardness tester used by the operator, but the higher hardness has no adverse effects on the finished product. The product still looks good, the disintegration is well within the established

[10] Comments are taken in part from the NNFA official comments for Docket No. 96N-0417

specifications, and the potency and identification of the dietary ingredients are unaffected. We read this regulation as restricting the quality unit's ability to release this product and think that such a restriction is not necessary.

This issue is compounded as well by the variable nature of many natural materials (such as herbals) for which specifications for tableting and encapsulation may vary. These specifications relating to things such as density and compressibility may need to be adjusted and can be adjusted without affecting the identity, purity, quality, strength and composition of the product as defined earlier in our comments.

Subpart E - Production and Process Controls

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

Testing for Contaminants[11]

Paragraph (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.

We recommend that this paragraph be incorporated into (e), relating to the establishment of specifications. This would help to simplify and clarify the testing requirements of this section and eliminate some of the redundancy.

[11] Comments are taken in full from the NNFA official comments for Docket No. 96N-0417

Subpart E - Production and Process Controls

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

Test Methods[12]

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

[12] Comments are taken in full from the NNFA official comments for Docket No. 96N-0417

Subpart E - Production and Process Controls

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

Recordkeeping[13]

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

[13] Comments are taken in full from the NNFA official comments for Docket No. 96N-0417

Subpart E - Production and Process Controls

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

Material Review[14]

Paragraph (n) directs companies to conduct a material review and disposition decision under paragraph (i) of this section. We think that this paragraph restates the requirement in §111.35(i)(2). It should be eliminated.

[14] Comments are taken in full from the NNFA official comments for Docket No. 96N-0417

Subpart E - Production and Process Controls

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

Animal-Derived Dietary Ingredients

The FDA is considering whether to require and has asked for comments on specific requirements designed to prevent the use of materials derived from certain animals from regions (BSE Countries) identified in 9 CFR 94.18 and has asked for input on this matter.

ANS does not believe that this document is appropriate for such a discussion. Placing specific requirements for the supplement industry in this document when regulations already exist is unnecessary.

As stated by the FDA in the opening sections, this document's purpose is to "establish the minimum current good manufacturing practices," and not to provide a new interpretation of DSHEA or other current existing regulations that span multiple industries.

Subpart E - Production and Process Controls

Section 111.37; What requirements apply to quality control?[15]

Paragraph (b) outlines the responsibilities of the quality unit. ANS recommends it be redrafted as follows:

(b) Your quality control unit must have the authority and responsibility to do the following::
(1) Approve or reject all process, specifications, controls, tests, and examinations , and deviations or modifications to them, that may affect the identity, purity, quality, strength, and composition of a dietary ingredient or dietary supplement; and
(2) Approve or reject all components, dietary ingredients, dietary supplements, packaging and labels based on conformance to established specifications; and
(3) Review and approve all master manufacturing records and all modifications to master manufacturing records; and
(4) Review and approve all batch production-related records; and
(5) Review and approve instrument and equipment calibration programs; and
(6) Review and approve all laboratory control processes, and testing results; and
(7) Review and approve all packaging and label records which includes approval for repackaging and relabeling, and approval for release for distribution; and
(8) Examine each batch of dietary ingredient or dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record: and
(9) Collect representative reserve samples of:
(i) Each lot of components, dietary ingredients, dietary supplements, packaging, and labels received to determine whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications;
(ii) Each batch of dietary ingredient or dietary supplement manufactured to determine, before releasing for distribution, whether the dietary ingredient or dietary supplement meets its

[15]Comments are taken in part from NNFA workgroup drafts

specifications for identity, purity, quality, strength, and composition.

(10) Keep the reserve samples collected per (i) and (ii) for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. When dietary ingredients or dietary supplements have an expiration date, you must keep reserve samples for 1 year beyond the expiration date of the ingredient or product or 3 years beyond the date of manufacture, which ever is longer. The reserve sample must:

(i) Be identified with the batch or lot number; and

(2) Consist of at least twice the quantity necessary for tests.

(11) Perform appropriate tests and examinations of:

(i) Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications;

(ii) Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record; and

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

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

(12) Review and approve all material review and disposition decisions; and

(13) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

ANS recommends that the detail in paragraph (b) be eliminated to lessen the burden of compliance and for purposes of clarity. A great deal of this information should be determined by the manufacturer as the quality unit responsibilities and tasks are defined within the company.

We have eliminated routine reviews and cross-referencing of related records during batch production record reviews. It is unnecessarily burdensome to require a QC unit to review and cross reference all receiving records, and equipment calibration, inspections and checks records for

materials and equipment related to each batch record (as currently required in (5) and (10)).

For example, the QC unit has already reviewed and approved components, dietary ingredients, packaging, and labels prior to their release and has used unique identifiers for these raw materials as they are recorded on related documentation and records, which allow traceability back to this documentation for review when necessary. All material review and disposition decisions must be documented and these will include the unique identifiers that tie them to particular raw or in process materials. Equipment maintenance and use logs provide necessary information should there be a reason to review this information per a particular batch record. Therefore ANS believes this cross referencing review is a redundant, particularly burdensome requirement and should be only be mandatory in cases where a specification has not been met.

Additionally, ANS has combined (7) & (8) into (5) and we have added language that addresses products with expiration dates as we believe that (12) should address reserve samples for samples with expiration dates to be consistent with our recommendation for 111.125.

ANS recommends eliminating (11)(ii), the requirement to collect and retain representative samples of in process materials. This exceeds sample collection and retention requirements in the drug GMPs and will create overly burdensome storage issues for the industry. In process samples typically are collected to monitor specifications such as tablet or capsule size, dissolution or disintegration, moisture content or composition. The purpose is to identify when these specifications are not met and address such issues during the production process. Due to the temporary nature of the issues being examined, these samples will usually not retain their characteristics over time, and those specifications relative to the finished product will be monitored in the finished product samples. Thus these samples have no value over an extended period of time. 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 GMP program.

Subpart E - Production and Process Controls

Section 111.45; What requirements apply to establishing a master manufacturing record?[16]

Section 111.45 established requirements for the preparation of master manufacturing records for dietary ingredients and dietary supplements. ANS recommends FDA redraft this sections as follows:

(a) You must prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement that you manufacture and for each batch size to ensure uniformity from batch to batch. The master manufacturing record must:

(1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration; and

(2) Establish controls and procedures to ensure that each batch of dietary ingredient or dietary supplement manufactured meets those specifications.

(b) The master manufacturing record must include the following information:

(1) The name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient per unit or portion, or per unit of weight or measure of the product, for each batch size;

(2) A complete list of components to be used;

(3) An accurate statement of the weight or measure of each component to be used;

(4) The identity and weight or measure of each dietary ingredient;

(5) A statement that explains any intentional excess amount of a dietary ingredient;

(6) A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at appropriate phases of manufacturing;

(7) A description of packaging and the label to be used; and

(8) Written instructions including, but not limited to, the following:

(i) Specifications for each point, step, or stage in manufacturing the dietary ingredient or dietary supplement necessary to prevent adulteration;

[16] Comments are taken in part from NNFA workgroup drafts

(ii) Sampling and testing procedures;
(iii) Specific actions necessary to perform and verify points, steps, or stages, necessary to meet specifications and otherwise prevent adulteration, including, but not limited to, one person weighing or measuring a component and another person verifying the weight or measure and one person adding the component and another person verifying the addition;
(iv) Special notations and precautions to be followed; and
(v) Procedures for use when a specification is not met.

(c) You must have the quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record.

(d) You must keep master manufacturing records in accordance with Sec. 111.125.

ANS recommends that (b)(1) include the name and weight or measure of each dietary ingredient or dietary supplement per unit or portion, or per unit of weight or measure of the product – per batch size. We believe this is an important product characterization that should be in the master manufacturing record and this requirement would be consistent with NNFA GMPs and the drug GMPs. ANS has eliminated the detail in (b)(4). All dietary ingredients are required by labeling regulation to be listed on the label of a dietary supplement as are all other ingredients present in the finished product. Manufacturers are responsible for meeting label claim and other labeling regulations by law – industry doesn't need to be burdened with extra paperwork requirements within the master manufacturing record. This is a section does not appear to provide additional control to the manufacturing process.

ANS has eliminated the detail (b)(6) because we believe it is more appropriate for the manufacturer of the product to identify and make decisions as where and when to include a statement of theoretical yield.

ANS has redrafted (b)(7) to require a description of packaging and the label to be used: The issue here is practicality. Many times companies do not have a label available, particularly contract manufacturers. We note that this is a requirement in the drug GMPs, but do not believe it is necessary for dietary supplements. A description of the label used in the master manufacturing record and a requirement to attach a copy of the label to batch record will provide the needed control.

ANS has modified this (b)(8)(v) to require procedures for use when a specification is not met. This is consistent with our earlier comments

opposing a requirement to establish corrective action plans throughout the manufacturing cycle. This gives the flexibility to cover the general categories in each situation where a specification is not met (to so per each specification is not possible given the considerable variables in this industry's manufacturing operations).

Subpart E - Production and Process Controls

Section 111.50; What requirements apply to establishing a batch production record?[17]

Paragraph 111.50 establishes requirements for the preparation and use of batch production records for dietary ingredients and dietary supplements. ANS recommends FDA redraft this section as follows:

(a) You must prepare a batch production record every time you manufacture a batch of a dietary ingredient or dietary supplement and the batch production record must include complete information relating to the production and control of each batch.

(b) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in producing the batch.

(c) The batch production record must include, but is not limited to, the following information:

(1) The batch, lot, or control number;

(2) Documentation at the time of performance, showing the date on which each step of the master manufacturing record was performed, and the initials of the persons performing each step, including but not limited to:

(i) The person responsible for weighing or measuring each component used in the batch; and

(ii) The person responsible for adding the component to the batch.

(3) The identity of equipment and processing lines used in producing the batch;

(4) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, if this information is not maintained in equipment logs;

(5) The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;

(6) The identity and weight or measure of each component used;

(7) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the weight or measure of each component used in the batch;

[17] Comments are taken in part from NNFA workgroup drafts

(8) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the addition of components to the batch;

(9) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(10) The actual test results for any testing performed during the batch production;

(11) Documentation that the dietary ingredient and dietary supplement meets specifications;

(12) Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;

(13) Description of any sampling performed;

(14) Any documented material review and disposition decision in accordance with Sec. 111.35(j) and 111.50(d)(1); and

(15) Signature of the quality control unit to document batch production record review and any approval for reprocessing or repackaging.

(d) The quality control unit must review in accordance with Sec. 111.37(b)(4) the batch production record established in paragraph (c) of this section.

(1) If a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record.

(e) The quality control unit must document in accordance with Sec. 111.37(c) the review performed in accordance with paragraph (d) of this section and it must be documented at the time of performance. The review and documentation must include, but is not limited to, the following:

(1) Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results;

(2) Identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master production record;

(3) Records of investigations, conclusions, and corrective actions performed in accordance with paragraph (d) of this section; and

(4) The identity of the person qualified by training and experience who performed the investigation in accordance with paragraph (d) of this section.

(f) You must not reprocess a batch that deviates from the master manufacturing record unless approved by the quality control unit. You must

not reprocess a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals;

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

(h) You must keep batch production records in accordance with Sec. 111.125.

ANS has added language to (c)(4) to eliminate this requirement if the cleaning and maintenance information is maintained in equipment logs. (b)(3) requires the identity of all equipment and processing lines used to be documented in the batch record which allows for traceability and review of equipment logs should it be necessary to review the maintenance, cleaning and sanitizing history of a piece of equipment or a processing line,. It is not necessary to routinely include such detail or documentation in a batch record and this requirement creates additional, unnecessary and redundant recordkeeping.

ANS suggests that FDA clarify what is meant in (b)(11) and (b)(12). As we stated in the comments for 111.25, we feel that it is overly burdensome to require companies to keep multiple instances of these logs within each batch report. A single lot of raw material may be used in hundreds of batches; test results taken upon receipt of this raw material need not be included in each batch file when it is kept on record and can be easily cross referenced and traced through each batch.

Also, what container labels are included in the requirement under (c)(12) this requirement? Does this relate to the finished product container labels, bulk material container labels, etc.? If so, ANS feels this is unnecessary to ensuring that the dosage form meets specifications.

ANS has eliminated (d)(2). Once again, ANS strongly objects to FDA attempt to restrict a company's ability to approve and release a batch of dietary ingredient or dietary supplement if an investigation or material review has been conducted and the product has been found acceptable by the QC unit. We have noted in our earlier comments that there instances where a product may be out of specifications in a way does not render it unsafe or mislabeled or unfit for consumer consumption.

ANS has eliminated the routine review required in (e)(1). This review is a redundant function, the QC unit has already performed a review of these

records when the components, dietary ingredient and/or dietary supplement were received and subsequently approved and released for use. The QC unit should only have to repeat this review if it is conducting an investigation or a material review following a deviation or should a specification not be met. This is a duplication of effort and a administrative and economic burden that adds no significant control or benefit to the GMP process.

ANS has redrafted (g) to allow for QC determination of reprocessing and the release of reprocessed batches for the reasons cited in comments related to 111.50(d)(2).

ANS has eliminated (h) as this requirement is an exact duplicate of 111.37(b)(11)&(12). We have replaced that requirement with a requirement to describe any sampling performed, inserted at (c)(12).

Subpart E - Production and Process Controls

Section 111.60; What requirements apply to laboratory operations?[18]

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

[18] Comments are taken in part from the NNFA official comments for Docket No. 96N-0417

Subpart E - Production and Process Controls

Section 111.70; What requirements apply to packaging and label operations

FDA states in §111.70(e) 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."

This should be redrafted to give the quality control unit the authority to make an appropriate disposition decision. As stated before, all product specifications may not affect the "identity, purity, quality, strength, and composition" of a dietary supplement.

III. Analysis of Economic Impacts

ANS disagrees greatly with the FDA's analysis of economic impacts. We believe that they have understated the costs that testing and implementation of GMPs will have on the industry, as well as overestimating greatly the amount of money saved to the consumer.

Criteria of company size as described by the FDA
Very small – fewer than 20 employees; median revenue uner $1 million
Small – 20 to 499 employees; median revenue $5 to $20 million
Large – 500 or more employees; median revenue $20 to $50 million

This places our company under the small category with the following costs:

Figure 1.

Cost per company						
	First Year			On-going		
-	FDA stated impact	NNFA stated impact	ANS estimated impact	FDA stated impact	NNFA stated impact	ANS estimated impact
Very Small	$ 62,000	$ 310,000		$ 38,000	$ 599,000	
Small	$ 261,360	$ 728,000	$1,655,000	$ 161,000	$ 1,248,000	$3,422,250
Large	$ 249,000	$ 3,297,000		$ 141,000	$ 5,868,000	

For reference, we have included the averages stated by NNFA in their individual survey which included Figure 2, the breakdown of the calculations shown in Figure 1.

Please note, the costs in Figure 2 are additional costs due to the proposed rules as they are now stated, with the excess of finished product testing for individual ingredients. The basis of these costs for ANS are compromised of the frequency of our current products we manufacture (Figure 3.) multiplied by average costs. These costs were acquired by averaging the lab tests for products manufactured per category by 3 independent labs.

Keep in mind as well that the estimates in Figure 3 are accounting for the fact that not every ingredient will be able to be so easily tested. Those prices reflect the individual raw material tests for individual raw ingredients. We

are unable to estimate the cost of validating an individual test for each individual ingredient as it reacts to each and every unique formulation that is produced.

Incredible amounts of time and money needed for tests per each unique formula will result in it being unfeasible to create multi-ingredient products without incurring great cost. This will also keep manufacturers from being able to produce as many custom formulations tailored for customer's individual needs, as the costs incurred will be far greater then the products would be able to be sold for in the market.

The irony is that the savings received by the customer in this scenario (due to less time spent trying to find a quality supplement), will be due to the loss of choice in the marketplace of many custom formulas that will become too costly to test. The increase in cost is far beyond the scope of being absorbed by manufacturers and distributors and will ultimately have to be passed on to the customer in order for the products to be on the market. At the increases this ruling will cause, it is doubtful these products will be purchased.

It is our hope that the FDA reviews the accuracy of it's figures and the necessity of their testing demands so that an environment can be created that accommodates flexible GMP standards that can prove beneficial to both the industry and the consumer. We urge FDA to look more closely at the successful industry programs currently in place, as well as the Food GMPs, for a model which has proven successful.

Figure 2.

Size of establishment in square feet:	66,000
Current Number of employees:	98
Full-time:	98
Part-time:	0
Number of batches produced annually:	3,100

Category:	**(one-time) Cost**	**Annual Cost**
Personnel (# FTEs)*		
New employees (excluding QC unit)	$ 20,000.00	$ 80,000.00
Minimum QC unit	$ 90,000.00	$ 574,000.00
Training	$ 24,000.00	$ 50,000.00
Personnel Sanitation	-	-
Facility Costs	-	-
Renovations	$ 175,000.00	-
Maintenance/Sanitation	-	-
Sanitation Supervisor	$ 25,000.00	$ 25,000.00
Pest Control	-	-
Production Equipment Costs		
Equipment (new/replacement)	not included	not included
Automatic Equipment	not included	not included
Equipment Calibration	not included	not included
Equipment Sanitation	not included	not included
Production Costs	not included	not included
Laboratory Equipment Costs		
Equipment (new/replacement)	$ 1,200,000.00	$ 100,000.00
Automatic Equipment	-	-
Equipment Calibration	-	$ 120,000.00
Equipment Sanitation	-	$ 30,000.00
Analytical Costs		
Method development	$ 84,000.00	$ 60,000.00
Increased testing ***(see figure 3)***	-	$ 2,277,650.00
Documentation and Recordkeeping		
Development of documentation	$ 20,000.00	$ 62,400.00
Training	$ 10,000.00	$ 32,000.00
Recordkeeping	$ 7,000.00	$ 31,200.00
Holding dietary ingredients/supplements	not included	not included
TOTAL BREAKDOWN	**$ 1,655,000.00**	**$ 3,442,250.00**

Figure 3

	# of dietary ingredients	# of total ingredients	# of tests	Average total cost of tests		Average batches per year		# of products in category		total
Non-vitamin / single ingredient	1	4	1+	$ 225.00	x	3	x	200	x	$ 135,000.00
Non-vitamin / 2-5 ingredients	4	8	5+	$ 915.00	x	3	x	150	x	$ 411,750.00
Non-vitamin / 5-10 ingredients	6	9	6+	$ 1,515.00	x	3	x	100	x	$ 454,500.00
Non-vitamin / 10-20 ingredients					x		x		x	
Non-vitamin / > 20 ingredients					x		x		x	
Vitamin, single ingredient	1	5	1+	$ 280.00	x	4	x	50	x	$ 56,000.00
Vitamin, 2-5 ingredients	2	8	4+	$ 700.00	x	4	x	100	x	$ 280,000.00
Vitamin, 5-10 ingredients					x		x		x	
Vitamin, 10-20 ingredients					x		x		x	
Vitamin, >20 ingredients	21	24	19+	$ 1,514.00	x	4	x	50	x	$ 302,800.00
Mixed, = to or < 20 ingredients	4	11	4+	$ 540.00	x	4	x	50	x	$ 108,000.00
Mixed, > 10 ingredients	19	26	20+	$ 2,648.00	x	4	x	50	x	$ 529,600.00