NSF International

1491 '03 AUG 11 P1:11

August 7, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: Docket No. 96N-0417

Our company, NSF International is involved in third party audits of dietary supplement manufacturing facilities. NSF International is fully supportive of FDA's effort to adopt Current Good Manufacturing Practices for the Dietary Ingredient and Dietary Supplement industry. Based on a review of the FDA's proposed cGMP's, our comments are as follows:

- **Supplier Responsibility:** The language used in the regulation and the Supplementary Information seems to minimize the supplier's responsibility in compliance with these cGMP's. Based on Section 111.1 *You are subject to the regulations in this part if you manufacture, package, or hold a dietary ingredient or dietary supplement.* Also, 111.6 Exclusions indicates that these cGMPs do not apply to a person engaged solely with the raw agricultural commodity. Therefore any facility that takes steps to process the raw agricultural commodity is then subject to these cGMPs. As such, there should be wording in the regulations to emphasize that the certificate of analysis that the cGMP compliant supplier provides with the dietary ingredient must have supporting documents (this would be part of their batch records in 111.50). To reinforce who is responsible for compliance with these cGMPs, Section 111.1 could be modified to additionally include the words "...suppliers, distributors, re-packers, warehouse, re-labelers and wholesalers...".

- **Written Procedures:** NSF International supports the requirement for development and use of written procedures by manufacturers in addition to record keeping requirements. The records document that quality control operations and processes were performed, but the written procedures give details such as how the task is to be performed, at what frequency it should be performed, etc. Both written procedures and records should be key components of the cGMP system.

- **Heavy Emphasis on Testing:** Section 111.35 *(g) You must ensure, through testing or examination, that each specification that you established under paragraph (e) of this section is met.* Where (e) reads in part *Specifications must be established for: (1) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive; ...*

96N-0417

C 165

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org

- The term "purity" to imply "without impurities" does not seem appropriate in the context of dietary ingredients. For example, it is difficult to consider an herbal extract as being "pure" since it is a mixture of naturally occurring compounds in a solvent. The term "strength" to imply "concentration, that is, the amount per unit of use intended" is also difficult to apply to some dietary ingredients. For example, the industry may have accepted marker compounds (or classes of marker compounds) for specific herbals but this is not the case for all dietary ingredients. Therefore, the definition of strength may need to be expanded on to make it more applicable to these situations. Suggested rewording would be "Specifications must be established: (1) Relating to identification, potential impurities, quality, strength (as applicable) and composition..."

- The focus on testing runs counter to the principle that "quality should be engineered into the process". The proposed cGMPs require final product testing, however, no amount of testing will correct quality problems at the end. Quality systems need to be developed to prevent problems early in the process (through proper training, procedures, raw material selection, etc.).

- The statements in the preamble (~p. 66-68) indicate that the manufacturer cannot utilize supplier certification and must perform their own testing. Based on the processing steps that a dietary ingredient goes through, the evidence that can be collected via testing may be weak and/or inconclusive versus assurances of quality that can be gained through a well-controlled and well-documented paper trail. As indicated on page 64, "The certificate of botanical identity would follow the material through the manufacturing process, thus creating a paper trail." Section 111.35 seems to disallow this approach, which in some cases would be an improved process for ensuring the production of a quality product. As an example, a manufacturer may purchase a processed herbal that is a blend of several herbal ingredients. Although the manufacturer should set acceptance specifications for this material, no scientifically valid analytical methods are likely to be available for this blend that could prove identity, purity, quality, strength, and composition of each ingredient in this blend. Allowing the manufacturer to utilize the supplier's certification (produced in a cGMP environment) and combining this with appropriate manufacturers specifications as determined by Hazard Analysis and Critical Control Points (HACCP) principles would be consistent and adequate to promote and protect the public health.

- On page 123 of the Supplementary Information, it states "Manufacturers that rely on supplier certification to ensure that materials derived from animals are BSE-free would likely need to verify the reliability of supplier certifications by conducting supplier audits at appropriate intervals." If supplier certifications can be verified and relied upon in this instance, why couldn't the same approach be

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org

taken for other parameters (as opposed to requiring testing)? For example, if a supplier has certified that an ingredient has been tested for pesticides, the cGMPs indicate that a manufacturer could not accept this; rather they would also need to test the ingredient themselves. This would lead to redundancy and a dramatic increase in the "cost of doing business" in the dietary supplement industry. End-of-the-line testing does not encourage quality "up the supply chain". The proposed regulation does not provide motivation for suppliers to be involved in 3rd party certification programs or to do thorough testing of their materials if this information cannot be used to support the quality programs of their customers. Finished product manufacturers would be less likely to be involved in 3rd party assessments of their operations and products because the available resources would be used up due to extensive in-house or directly contracted testing. Our recommendation is that "verifying the reliability of supplier certifications by conducting supplier audits at appropriate intervals" should be an acceptable practice available to facilities operating under cGMPs.

- The section requires testing of each lot for each parameter on the basis of identity, purity, quality, strength, and composition. Therefore, a manufacturer of a multivitamin would be required to test for each ingredient in the finished product (or in the ingredient received if no methods are available for the finished product). The amount of testing could be quite extensive and costly. Alternate quality approaches of establishing acceptance specifications for ingredients with random or representative testing are apparently not allowed. Nor does it seem acceptable to set finished product specification on only a subset of parameters deemed critical through a HACCP analysis. Allowing the manufacturer to define and implement critical control measures which impact the quality of the ingredients and products produced would be preferable over prescribed extensive finished product testing.

- **Scientifically Valid Analytical Methods:** The proposed cGMP regulations should clearly define or more clearly interpret what is meant by "scientifically valid analytical methods". It is recommended that the definition be included under section 111.3.
  - In the Supplementary Information (p.34), it discusses what is meant by "officially validated methods" and AOAC methods are given as an example. Page 62 indicates "the use of a standard compendial method, such as those published by the USP or AOAC International." Because of the evolving nature of methodology for ingredients used in dietary supplements, FDA should provide industry with more guidance as to what can be considered authoritative for the purpose of compliance with cGMPs. The examples for sources of methods that have been validated by independent testing in separate laboratories under identical conditions should be expanded to include methods from the Institute for Nutraceutical Advancement (INA), American Herbal Pharmacopoeia (AHP), European Pharmacopoeia and the World Health

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org

Organization. In the Supplementary Information (p.221), a scientifically valid analytical method is described as "one that is based on scientific data or results published in, for example, scientific journals, references, text books, or proprietary research". It should be noted that a published method may be valid in the context it was used it cannot be automatically assume that this method will work for a finished product which very often has a combination of ingredients making the sample matrix unique. This situation requires the manufacturer's laboratory or subcontract laboratory to evaluate the validity of the method for this unique sample matrix. How the information gained by the method is to be used will dictate the elements that would need to be evaluated to consider the method as "valid".

- A proposed definition/interpretation for "scientifically valid analytical method" is "one that is based on scientific data or results demonstrating that the method is fit for the intended purpose. The source of the method may include AOAC International, USP, Institute for Nutraceutical Advancement (INA), American Herbal Pharmacopoeia (AHP), European Pharmacopoeia, World Health Organization, ISO, etc., as well as, scientific journals, references, text books, proprietary and non-proprietary research. The scientific data would show the specificity, reproducibility, linearity, recovery and method detection limit of the method as applicable within the context of how and why the method is used."

- **Animal-Derived Dietary Ingredients:** NSF International considers these ingredients to be well within the scope of the proposed cGMPs and does not believe there should be specific cGMP requirements for this category of materials. Consistent with the proposed cGMPs, suppliers and manufacturers should develop specifications and institute other critical control measures to prevent potential adulteration linked to specific risks to public health.

- **Expiration Dating:** The final rule should require expiration dating and stability testing. These dates shall be supported by data and/or rationale to reasonably assure the product meets the manufacturer's established specifications throughout the product shelf life. Accelerated stability studies or data from similar product formulations may be used for an initial determination of shelf life. Product shelf life may be confirmed and may be extended on the basis or real-time studies on product stored under labeled storage conditions.

- **Grounds:** A section should be included for "Grounds" which is consistent with Food cGMPs (Section 110.20(a)). This section indicates that the "grounds of a manufacturing plant shall be kept in a condition that protects against adulteration of product." The section gives methods to be included. Just as this is important to a facility manufacturing food, it is equally important to a facility manufacturing dietary supplements.

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org

- **Section 111.65 (c)(5):** In the Advanced Notice of Proposed Rulemaking, this section read "Measures such as sterilization, irradiating, pasteurizing, freezing, refrigerating, controlling pH...are taken to destroy or prevent growth...shall be adequate." In the current proposed cGMPs, the term irradiating has been removed, and the statement, "or using any other effective means to remove..." has been added. It is recommended that the term "irradiating" is left in the final rule to remove any doubt that irradiation can be used.

- **Section 111.45 (a)(8)(iii):** This section reads "Specific action necessary to perform and verify...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". This language is overly prescriptive. The manufacturer should be able to design a verification/check system specific to their operation. For example, one scale could be used to weigh the component and a scale on the vat could confirm this addition. It is recommended that the phrase "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" be eliminated from this section. Likewise, 111.50 (b)(7) & (8) require initials of the person responsible for verifying the weight, measure or addition. Again, this level of detail does not give adequate flexibility in how the manufacturer chooses to prevent adulteration.

General Comments: In keeping with the spirit of The National Technology Transfer and Advancement Act of 1995 we believe a compliance program to enforce dietary supplement cGMPs that includes the use of third party conformity assessment bodies will benefit stakeholders, including consumers, FDA and responsible members of the industry. The third party system can assist FDA and industry in assuring compliance and reduce the burden on FDA to implement the regulations in the following ways:

- They provide third party independent assurance that ingredient suppliers and supplement manufacturers meet minimum system and testing requirements.
- By allowing efficient utilization of existing resources by the FDA. For instance, responsible manufacturers and suppliers utilizing services from recognized third party providers may merit reduced monitoring by FDA. Agency resources are then available to focus on companies that are clearly operating outside of the law.

The use of third party conformity assessment services by federal agencies has a proven and successful track record and is encouraged through legislation. NSF respectfully requests FDA use third party systems in to implement and promote compliance with final cGMP rules. It is our announced intention to incorporate the cGMP rules into our standard for dietary supplements, NSF/ANSI 173, now an American National Standard, upon their adoption. We both stand ready to work with the FDA in developing a system that can provide maximum benefits to all

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org

stakeholders while ensuring full compliance with the regulations and protection of the public health.

NSF International appreciates FDA's consideration of our comments as they move toward adoption of final cGMP rules for the dietary supplement industry.

Respectfully,

Kathleen J. Pompliano

Kathleen J. Pompliano, MS, RD
NSF International

P.O. Box 130140 Ann Arbor, MI 48113-0140 USA
734-769-8010 1-800-NSF-MARK Fax 734-769-0109
E-Mail: info@nsf.org Web:http://www.nsf.org