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

RE: Docket No. 96N-0417; Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements.

Dear FDA Administrator,

My company supports the establishment of current good manufacturing practices (cGMPs) rules for dietary supplements. Responsible companies in the industry, like ours, already have effective programs in place that allow us to ensure product integrity as described in your proposed regulation. However, I am concerned that even responsible companies will be faced with costs beyond FDA's estimate due to an especially rigid and unnecessarily burdensome testing scheme and fundamental miscalculations made by the agency in its economic analysis on the impact of the proposed rule.

As you are aware, the nutriceutical industry has always been regulated by the FDA under the food category and not drug. With the release of these new cGMP rules for the nutriceutical industry, we are concerned that you are applying a revised set of cGMPs from the pharmaceutical industry to this relatively new industry. I am sure you realize the impact this would have on the future growth of the industry. Established pharmas will have no trouble since they are already in place making drugs. Smaller supplement companies would require considerable investment in personnel, time and monies to just catch up.

The following factors are critical to achieve a workable cGMP regulation for nutriceuticals: 1) supplement cGMPs should apply to the entire industry; 2) an appropriate testing regime should be required, including the use of certificates of analysis, and testing at appropriate points during the manufacturing process to include statistically-based batch testing options; 3) FDA should modify sections of its proposal to be more flexible and/or to include the existing industry standard; and 4) FDA should require written procedures for certain operations, and documentation if appropriate, in key areas.

We also believe that 1) expiration or shelf-life dating should be required on product labels; 2) economic costs outlined by FDA are grossly underestimated and will have a significant and detrimental impact on the dietary supplement industry; particularly the "small and very small" as defined by FDA; and 3) the compliance periods that FDA has proposed may not allow small entities adequate time to implement the rule. Our comments follow.

Supplement cGMPs Should Apply to the Entire Industry

We support the FDA's proposal that this rule should apply to the entire industry, including foreign firms and raw material manufacturers. Broad application of the rule offers an additional layer of

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assurance that products have the identity, purity, quality, strength and composition they purport to have. Establishing that ingredients meet specification in a reliable manner at the beginning of the process, and then maintaining quality through appropriate process controls by manufacturers is an effective and efficient manner to assure quality. We have a major concern when it comes to the implimentation of the cGMPs internationally. Over 50% or more of the ingredients in the nutriceutical industry comes from overseas. How will foreign firms meet American cGMPs? Will the FDA inspect all ingredient suppliers around the world? Where is the enforcement to take place? It would be a major disserve if this happens at the border?

Currently, there are thousands of ingredients without established testing protocols or product standards that have always been treated as foods. How can the FDA enforce cGMPs where there are no agreed upon testing procedures? Raw ingredient manufacturers are the only entities in the supply chain in some instances, such as with some botanicals or unique formulations, with the expertise to evaluate a raw material. We believe that by building more flexibility into some sections of the rule, bulk ingredient manufacturers that supply ingredients to the nutriceutical industry will be able to comply without major changes to their processes or equipment. By building in a longer-term approach and requiring the reporting of product data and testing protocols, the FDA will gain the tools to conduct a successful nutriceutical verification program.

An Appropriate Testing Regime Should be Required

We support the recommendations of the National Nutritional Foods Association that FDA adopt a more appropriate testing scheme to reduce the number of unnecessary tests required under the proposed rule. Flexibility in some critical areas, such as when, how and how often to test components, dietary ingredients and dietary supplements against established specifications, will allow time to develop a cGMP program that meets the mandates of the rule while still providing necessary controls. We believe these changes will lessen the economic impact and burdensomeness of the proposed rule to an acceptable level without compromising the legitimate goals of cGMPs.

The proposed rule appears to rely on an unnecessarily exhaustive and rigid testing scheme. As drafted and interpreted by virtually the entire industry, the proposed rule requires manufacturers to test every batch of finished product, if possible. In most cases, there are so many active ingredients that this would be impossible. If it is not possible to test the finished product, then the verification of the dietary ingredients need to be conducted. Third party certificates of analysis from qualified ingredient suppliers should be accepted and, if not available, supplement manufacturers would be required to test upon receipt. Testing need not be performed at every level of the supply chain.

Although FDA has presented this proposal as flexible, we are concerned it will eliminate many products from the marketplace that have been safety used for long periods of time. This clearly goes against the spirit and intent of the Dietary Supplement Health and Education Act (DSHEA) of 1994. The FDA needs to take into consideration the safety record of nutritional supplements. According to the US Centers for Disease Control (CDC), deaths from supplements have average fewer than five confirmed deaths per year over the last 25 years. In contrast, "properly" tested, approved, regulated, and prescribed drugs are the fourth most common cause of death in the US

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killing in the 150,000 range. Applying drug-testing cGMPs for public safety reasons to nutritional supplements make absolutely no pragmatic sense. We support changes in product testing to recognize verified certificates of analysis, to allow for a statistically based approach to finished product testing, and not require unnecessarily redundant testing throughout the supply chain.

Verified Certificates of Analysis

FDA must allow for the use of verified certificates of analysis to show scientifically valid analytical testing has been conducted. Certificates of analysis are a key component of the manufacturing process, used by similar industries, and there is simply no economically feasible alternative. The final rule should require that ingredient supplier's certificates of analysis verified by a qualified third-party testing laboratory be adequate proof under nutriceutical cGMPs. Supplement manufacturers should be required to confirm the veracity of information provided using random statistical testing at appropriate intervals. Companies should not be required to do site inspections of their supplier's factories.

Frequency and Feasibility of Testing

We agree that testing is necessary. However, we support the testing of dietary ingredients and supplements for conformity to specification based on a frequency that has been established under a statistically valid method to ensure in-process controls are adequate to assure the identity, purity, quality, strength and composition of individual dietary ingredients or dietary supplements. The availability of test methodology and the appropriateness of various points for testing dietary ingredients (i.e. identity, raw material, in-process or in the finished product) are still in the developmental stages on many ingredients.

Testing Responsibilities

The proposed regulation does not clarify what testing obligations different companies, with different roles, have in the supply chain. We recommend that the final regulation make it clear that testing obligations fall primarily upon the ingredient supplier of the raw material and on the supplement manufacturer of the finished dosage form and that only one company in the chain has to perform the appropriate testing. For instance, companies that merely bottle or label finished product need not be held responsible for potency, identity, and purity.

Supplement cGMPs Should be More Flexible

The proposed rule lacks appropriate flexibility in areas where general direction would suffice to produce safe and accurately labeled products. In most instances, more reasonable and effective alternatives are already being used by industry. The following examples illustrate the type of flexibility we are requesting.

- Companies need flexibility to design appropriate and effective testing regimes. For instance if a raw ingredient is tested upon receipt, it likely does not need to be re-tested for those same specifications when it is incorporated into multiple products.

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- Companies need the flexibility to incorporate a statistical approach to finished product testing. Statistical testing provides necessary control as the consistency of test results and manufacturing processes are verified. First, through initial tests for conformity; and then once conformity is established, manufacturers then have the option to reduce the amount and frequency of testing based on the attributes of both the product and manufacturing process.

- Companies need flexibility to design manufacturing facilities to suit their operation. We believe, for instance, that ceiling surface is irrelevant to manufacturing processes which are completely enclosed. Moreover, manufacturers that are working with ingredients that are not hygroscopic, such as calcium, or in areas with low humidity, may not need to install equipment to control humidity.

- Section 111.65 is a good model as to an appropriate level of flexibility. This section, which covers requirements that apply to manufacturing operations, clearly states the requirements and presents relevant factors that must be considered when determining how to best meet the mandate of the rule. It is not overly prescriptive.

Written Procedures and Documentation Should be Required in Key Areas

FDA has excluded the use of written procedures and documentation from its proposal in some key areas where existing industry standards require them. Written procedures and documentation are key in-process controls. We suggest they are necessary in the following areas: 1) cleaning and maintaining equipment; 2) individual equipment logs; 3) responsibilities and procedures applicable to the quality control unit; 4) lab records; 5) raw material handling and testing; 6) reprocessing of batches; 7) packaging and labeling; and 8) handling complaints. Written procedures are vital to ensure uniform process control, and that employees are properly trained and supervised. They also provide an effective basis for FDA to assess the adequacy of a manufacturer's cGMP program. FDA should modify their proposal accordingly.

Expiration Dating/Shelf-Life Dating

FDA has declined to require expiration or shelf life dating on dietary supplement ingredients. We disagree, however, and believe that the final rule should require expiration or shelf life dating to appear on product labels. Consumers have come to expect an expiration or "best before" date on food products and we believe this can be accomplished without unduly burdening manufacturers. We recommend that FDA include the following paragraph, which is based on a requirement from the NNFA GMP program, within the final rule:

> (a) All products must bear an expiration date or a statement of product shelf life. Expiration dates or a statement of product shelf life must be supported by data to assure that the product meets established specifications throughout the product shelf life. Such data may include, but is not limited to:

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(1) A written assessment of stability based at least on testing or examination of the product for compatibility of the ingredients, and based on marketing experience with the product to indicate that there is no degradation of the product; or,
(2) Real time studies, accelerated stability studies or data from similar product formulations.

(b) Evaluation of stability shall be based on the same container-closure system in which the product is being marketed.

Economic Impact

The economic costs outlined by FDA are grossly underestimated. The economic and financial impact of the proposed rule will have a significant and detrimental impact on the dietary supplement industry. Most adversely affected will be very small and small (as defined by the FDA) establishments. FDA officials stated during a public meeting to explain their proposed rule, held in Oakland, California on May 6, 2003, that the rule would put approximately 250 companies out of business. We have been informed by NNFA, however, that based on their research this number is probably much higher. Many products, especially multi-ingredient products, will no longer be economical to manufacture and will disappear from retailers' shelves. We understand that prices of the products that remain will increase considerably.

Responsible companies in the industry have effective testing programs in place. But we are concerned that even responsible companies will be faced with costs beyond FDA's estimate. FDA has miscalculated costs most significantly by underestimating the (a) the number of batches produced by companies per year; (b) the cost to perform specific analytical tests; and (c) the number of tests that would need to be required under the proposal.

Adopting a more reasonable economic burden on companies, especially by decreasing the testing burden on the bottler, packager and distributor, would give companies more flexibility to develop testing programs around established specifications. Allowing companies to rely on verified certificates of analysis reduces the testing burden on companies. Allowing a statistical approach to finished product testing, along will allowing more flexibility in general, will also reduce costs.

Implementation of the Rule

FDA proposes allowing large companies one year, small companies two years, and very small firms three years to comply with the final rule. We do not support these compliance periods that FDA has proposed unless the rules are modified. Most of the companies in the nutriceutical industry will never be able to support the staff and investment required under the proposed rules. If the rules are modified, these time period may make sense.

We agree that a longer compliance period will reduce the significant economic impact on very small and small companies because they will have additional time to set up recordkeeping systems, make capital improvements to the physical plant, purchase new or replacement equipment, and other one-time expenditures. Further, products supplied by small companies are vital to the diversity, quality and price of products in a health food store, where most of these brands are carried. Consumers

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want these quality products, which are familiar to them and essential to retailers in the natural products industry, to remain available.

Conclusion

Finally, our company fully supports appropriate cGMP rules for nutriceutical industry covering both ingredients and supplement manufacturers. We recommend that FDA modify the proposed rule so that an appropriate testing regime is adopted and to require written procedures and documentation in some critical areas. Companies also need more flexibility to meet the mandates of the rule. These recommendations will lower the economic burden of this rule to a level which responsible companies in the nutriceutical industry will be able to comply without compromising the legitimate goals of cGMPs. Consumer can also be assured that safe and affordable nutritional supplement products from a variety of manufacturers remain available.

We urge FDA to give full consideration to our comments while also acting swiftly to issue a final rule that is not overly burdensome and will allow the industry to continue to provide consumers with a wide variety of safe, affordable, and high-quality nutritional supplements.

Sincerely,

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