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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 96N-0417
Good Manufacturing Practices for Dietary Supplements

These comments are submitted by Morinda, Inc., a manufacturer and distributor of Dietary Supplements. Since almost all of our sales are derived from Dietary Supplements, the proposed GMP regulations will directly effect our viability as a business entity.

We should state from the outset that we are, and will continue to place the highest importance on the safety, quality, and efficacy of our products. We support continued efforts to raise the standard of not only our products and processes but those of our industry. DSHEA has had, and will continue to improve Dietary Supplement quality.

Congress recognized the differences between foods, Dietary Supplements, and drugs. They understood that Dietary Supplements, due to their nature, use, and history are much more closely aligned to foods than to drugs. The industry in general, and our company specifically, are in favor of GMPs that will provide

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quality and safety of our products. As an industry we have spent a great deal of money and effort in drafting and implementing procedures that will meet the spirit of DSHEA and the needs of our consumers. However, in responding to the proposed GMPs, we feel that there are two fundamental areas so flawed that it mandates complete reevaluation of the document. These areas are: the failure to follow the basic mandate of DSHEA to model Dietary Supplement GMPs after food GMPs, and that the economic impact was grossly underestimated.

In this proposed rule, the agency published a very lengthy preamble detailing its rationale for this regulation and requested comments on at least 86 specific points. We believe that many of these questions can be consolidated into a smaller set of "issues" which will be the basis of these comments.

"We also recognize that the Council for Responsible Nutrition (CRN), the National Nutritional Foods Association (NNFA), the Utah Natural Products Alliance (UNPA), and the American Herbal Products Association (AHPA) will be filing comments which will cover, in detail, many of the 86 specific points raised by the agency.

1. **Legal Authority to Issue this Proposed Regulation.**

With respect to FDA's request for comments on the agency's legal authority to issue this regulation, we fully endorse the need for rigorous and adequate dietary supplement GMPs modeled on cGMPs for conventional foods.

Independently, and through trade organizations, the industry has done much to improve quality and safety of Dietary Supplements. We wish to affirm full support for the issuance of final GMP regulations, which will serve both the industry and its consumers.

We do not, however, believe that the agency has either a Congressional mandate or legal authority to propose or issue dietary supplement GMPs that deviate in material respects from food GMPs. Section 403(g)(2) of DSHEA states that GMP regulations "shall be modeled after current good manufacturing practice regulations for foods..." FDA defines "modeled" as meaning "a preliminary pattern" for DS GMPs and also has created a new working concept/definition for "dietary supplement" that would treat dietary supplements and ingredients as a "hybrid" regulatory category which combines aspects of both food and drug regulation due to the "characteristics and hazards" of dietary supplements. Using this new concept, the agency argues that Congress intended to grant the agency authority to establish regulations in this rule that do not have parallel provisions under food cGMPs. The basis for this theory is the agency's reliance on a single dictionary definition of "modeled" as a "preliminary pattern" to justify inclusion of drug GMPs. In fact, the Senate report of the 103rd Congress 2d Session is very clear as to their intent.

> "FDA is granted authority to promulgate good manufacturing practice regulations for dietary supplements provided such regulations do not impose standards for which there is no current and generally available analytical methodology... Given the FDA's historical bias against dietary supplements, the Committee believes it is necessary to place the above limitations on FDA's authority to promulgate GMP regulations."
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> "Under current law, dietary supplements are regulated as foods and need comply only with very general food GMP regulations. This section adds to FDA's enforcement authority to issue GMP regulations, after notice and comment, specific to dietary supplements. **These shall be in accordance with food, not drug, GMP concepts** and shall not require analytical data that is not currently and practically available to industry companies."

There are 51 dictionaries with English definitions for the word "model" and 15 dictionaries with English definitions for "modeled" (OneLook.com). Of these definitions, the principal definitions are:

- A plan or form after a pattern.
- To produce a representation or simulation.
- To construct or fashion in imitation of a particular model.

We believes that the clear language of DSHEA, coupled with the general definitions of model/modeled lead to one conclusion: that FDA's authority to issue this regulation must follow the pattern and intent of food GMPs to the exclusion of any other type of GMPs which FDA has or may issue. We also believe that the concerns expressed by the agency with respect to the safety of dietary supplements can all be addressed within the construct of food GMPs, as will be noted later. In summary, we do not believe that the agency has the legal

authority to issue a final regulation for dietary supplement good manufacturing practices that include in material or significant ways provisions from drug, medical device or other GMPs.

2. **Economic Impact on the DS Industry and Small Business in Particular.**

We believe that the agency has profoundly miscalculated the cost of compliance with this proposed regulation. Our preliminary analysis suggests that the costs to industry to comply with this proposed rule will be at least 50 times greater than that projected by FDA. We recognize that the agency noted in this proposed rule that it lacks adequate data to accurately calculate costs associated with compliance to small business in particular and other DS businesses generally. Our continuing research suggests that the costs associated with finished product testing alone are at least 100 times greater than that estimated by FDA. We have consulted with the owner and principal of Plant BioActives, Inc., which is cited by FDA as reference No. E51 as one of two references to calculate testing costs. FDA estimates the average cost of an analytical test to be $60. Our data indicates testing costs will range between $180-360 per test (see attachment No. 1). This does not include testing costs associated with finished raw materials or the cost to develop finished product testing methods, which would range from $50,000 to $100,000 per product if, in fact, it is possible to create a finished product test for complex multi-

ingredient finished product. Through the UNPA we are actively collecting additional data to assess, more accurately, costs associated with raw material and finished product testing, and support the UNPA request for additional time to present additional data after the comment period closes. We underscore our view that extensive finished product testing is not appropriate. Rather, we propose that rigorous raw material testing be developed, together with statistical sampling of finished raw materials, and be implemented along with an effective vendor certification program, as the appropriate means to assure product quality, purity and safety. This agrees with modern quality practices. Edward W. Demming, considered to be the father of modern quality engineering stated that US industry should "Cease dependence on inspection to achieve quality. Eliminate the need for inspection on a mass basis by building quality into the product in the first place...Quality comes not from inspection, but from improvement of the production process". We feel that more limited testing than has been proposed, but more effective certification and procedure control will result in greater quality and safety.

3. **FDA's Explanation and Rationale for this Proposed Rule – Protection of Public Health.**

We wish to express our surprise and concern with respect to the reasons stated by the agency for dietary supplement cGMPs. Shortly after passage of DSHEA in late 1994, the four major dietary supplement trade associations met

with FDA to discuss the need for good manufacturing practices. It was agreed that the DS industry would jointly prepare a framework for GMPs, which was shared with FDA. FDA published this framework on February 6, 1997 as an ANPR with additional questions raised by the agency to obtain comment on related issues. Nearly six years later, FDA published this rule, which virtually ignores the prior ANPR framework but rather stresses public health concerns based on several examples of adulterated, misbranded or mislabeled dietary supplements. The language of the preamble implies that dietary supplements are not subject to regulation by FDA, and that the stated examples of adulteration are a result of the agency's apparent inability to inspect, regulate or enforce current cGMPs for food, to which all dietary supplement products are subject. At the April 29, 2003 public meeting at FDA's offices in College Park, Maryland, one FDA official stated that conventional food GMPs are based on the principle of sanitation, whereas this proposed dietary supplement GMP regulation is based on a principle of prevention and avoidance of adulteration. We object to the pejorative characterization of dietary supplements as a public health risk and that the need for this regulation is based on the avoidance of adulteration of dietary supplements by imposing manufacturing practices which far exceed food GMPs.

4. **Subset GMPs for Dietary Supplements.**

The definition of dietary supplement includes a broad array of substances such as vitamins, minerals, botanicals and other agricultural materials, animal tissues, marine products, probiotics and other substances. These materials also range from synthetic fine bulk chemicals to complex plant extracts. The expertise, available analytical methods and production requirements and associated expenses to assure consistent quality and safety for these various materials are profoundly different. We believe the agency should take these differences into account by developing, in cooperation with industry, subset GMPs for those dietary supplement categories (principally vitamins and minerals, botanicals, fermented or live culture products) in order to minimize unnecessary expense while providing sufficient regulatory guidance on key issues such as testing needs and requirements, microbiological management, animal tissue handling and processing, temperature and humidity controls, performance testing (as appropriate).

We envision general dietary supplement GMPs which apply to all DS manufacturers together with any subset GMPs relevant to the products being produced and/or manufactured by individual companies. We note there is precedent within food GMPs to provide specific guidance of this type including low acid canned foods, bottled water and infant formula. We do not believe it

is advisable or practical for the agency to propose or implement DS GMPs that are so broad as to fail in giving adequate notice and guidance for specific GMPs in areas as described above. We do believe that industry would value and support having more specific guidance that would help provide both a clear GMP standard for manufacturers and FDA inspectors who have the responsibility to assure compliance with this regulation. We strongly urge the agency to establish dietary supplement GMPs under the framework of food GMPs together with additional requirements that serve to assure the safety, potency and purity of DS products.

5. **All Dietary and Other Ingredients Must be Lawfully Sold.**

FDA's proposed 21 CFR 111.35(d) would require that all non-dietary ingredient components be either:

- Authorized for use as a food additive;
- Authorized by prior sanction;
- If used as a color additive, used in accordance with a listing the includes use in dietary supplements; or
- GRAS.

FDA states in the preamble that any claim that a substance is GRAS "must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or a dietary supplement. Further, you could not use our

(FDA) response to your GRAS notification as your basis for asserting compliance with the requirements in Section 111.35(d), because an FDA response letter to a GRAS notification is not the same as your explanation for why an ingredient is GRAS."

We note and agree with the comments filed by the International Food Additives Council and the Calorie Control Council that also express concerns with respect to the agency's position on reliance of a supplier's determination that a substance is GRAS.

We are also deeply concerned that this proposed requirement not only contradicts the general practice and purpose of GRAS affirmation/notification but also would create deep confusion and uncertainty as to when a substance is indeed GRAS affirmed or otherwise lawfully sold in dietary supplements. Moreover, a number of substances with a well-known history of use in foods as well as drugs, and which are currently used in dietary supplements, would be left in a state of regulatory uncertainty. This matter is of particular importance for dietary ingredients, which are recognized as "grandfathered" or old dietary ingredients but which do not, in many cases, enjoy GRAS affirmed status. We believe the agency should clarify and correct its proposed language to confirm that GRAS affirmation/notification is both appropriate and encouraged. We also believe there is an urgent need to harmonize international excipient

standards with respect to safety and use to avoid major economic disruption and burdens on companies that have developed and are using safe and well tested substances which may be present in dietary supplement formulations.

6. **Consumer Complaints.**

The agency proposes a confusing and difficult scheme to review, investigate and resolve customer complaints that would require extensive human resources, record keeping and decision-making as to what is a consumer complaint versus an adverse event report. The definitions used is this section are broad and confusing at best. Additionally, there is no precedent for this requirement under cGMPs for foods. (See comment under Section I above.) Moreover, we believe that the issue of consumer complaints and adverse event reporting are important and relevant to all conventional foods (as well as dietary supplements) and cosmetics.

We support the development of a comprehensive system to track and analyze adverse event reports now under development within CFSAN. This new CFSAN Adverse Event Reporting System (CAERS) should replace the current patchwork of existing adverse event reporting systems. We are concerned that the agency's proposal to develop a consumer complaint adverse event reporting system, specific for dietary supplements, contradicts the overall

objective of CAERS, which is to develop a harmonized system for foods, cosmetics and dietary supplements.

We therefore suggest that this section be removed from this GMP proposal and be dealt with under the developing CAERS system.

7. **Testing of Raw Materials and Finished Products.**

FDA proposes that all finished product be tested to confirm that specifications for identity, purity, quality, strength and composition are met, provided there are scientifically valid analytical methods available to conduct such testing. Where this cannot be done, each shipment lot of components, dietary ingredients or dietary supplements must be tested to confirm identity, purity, quality, strength and composition of such materials. We object to this proposal on three grounds:

- In many cases, there are not yet scientifically valid analytical methods to test finished products, especially botanicals. Accordingly, companies would be subjected to the enormous burden of developing finished product testing methods for hundreds, if not thousands, of products at an estimated cost of $25,000-50,000 per finished product validation method. We have received advice from a number of analytical laboratories that for complex multi-ingredient products, this price could easily double, if it is even possible to develop a multi-ingredient finished product test.

- FDA places great reliance on finished product testing on the apparent belief that it is possible to test-in quality to a dietary supplement product. It is our view that quality should be built into and not tested into products, and the heavy emphasis on finished product testing places the emphasis at the wrong stage of manufacturing and

production.

- The cost burden to test finished product is economically unfeasible for both large and small companies. The majority of dietary supplement products contain multiple ingredients, which makes finished product testing exceptionally difficult and expensive. Two of our member companies have developed economic models assuming they tested every ingredient in all finished products for conformance to this provision.

FDA estimates the average analytical test will cost $60. Our research indicates the average cost of an analytical test to be between $165-300. Heavy metal testing ranges from $45-180 per test for lead (depending on the technique and method used). Microbiological testing using AOAC methods for aerobic plate count, E. coli, yeast and mold, staph a., salmonella, listeria: $200. Pesticide testing – multi-residue screen: $550.

In our case, the average number of ingredients per product is about 23, with some having as many as 63. Reviewing the price structure from 5 reputable laboratories in the drug and dietary supplement industry the average cost per analysis is about $200. The cost of testing just one parameter per ingredient would average $46,000 per lot. This does not include multiple tests required for most ingredients (heavy metals, three or more specific microbiological examinations, pesticides or other hazards that are not clearly defined). This additional testing will easily double the cost of analysis for us to nearly $100,000 dollars. When increased raw material costs due to increased

testing costs for suppliers, and reduced competition because of imposed economic failure, this cost could potentially be much higher. We will also have a reduced customer base because few consumers will be able to afford our products. Obviously, the burden of the proposed level of testing would likely force us out of business.

We believe that FDA has drastically underestimated the cost of testing for finished and raw materials. We also believe the economic impact and burden imposed by FDA's proposed finished product testing requirements to be so significant as to cause more than 50% of all small businesses to cease operations and render a significant number of medium and large businesses economically crippled. Currently it is estimated that 158,000,000 Americans regularly use Dietary Supplements. The likely result would be to make these products unavailable to large segments of the population. The increased costs of manufacturing dietary supplements under the proposed GMPs would force companies currently manufacturing for export to move production off shore. For the above reasons we therefore believe FDA's economic analysis is deeply flawed and must be comprehensively reevaluated.

We are seeking additional economic data used by FDA to develop its economic model for this regulation, which we have not yet received. We are also working with the State of Utah's Department of Community and Economic

Development to further develop an economic impact assessment of this provision on Utah industry.

8. Certified Vendor Programs.

We strongly believe that the most effective means to assure that DS/DI conform to specifications for identity, purity, quality, strength and composition are to develop rigorous certified vendor programs which require vendors of both DI/DS to demonstrate, by a certificate of analysis and a vendor screening and management program, conformance to specifications. This would include vendor audits, inspections and verification and acceptance procedures. The general food GMPs in 21 CFR 110 specifically allow the use of certificates of analysis to verify that ingredients meet their requirements for safety, microorganism content and conformity to toxin, pests and extraneous materials levels. We also support in-bound raw material testing be a requirement, together with any necessary in-process testing requirements as appropriate.

We further believe that industry should, as a matter of GMP best practices, develop harmonized certificates of analysis that would include all necessary information to provide the purchaser of the dietary ingredient or supplement to confirm conformance to specifications.

We note that FDA requested comment on whether this proposed regulation should apply to foreign manufacturers of dietary ingredients and dietary

supplements (DI/DS). We believe that all companies, domestic and foreign, should be held to the same standard of GMP requirements. However, given lack of FDA's jurisdiction over many foreign manufacturers and suppliers of dietary ingredients and supplements, it is essential that the principal obligation to assure conformity to specifications rests with the purchaser of DI/DS, which is best accomplished by a rigorous vendor certification program.

9. **Implementation.**

The agency proposes a three-year tiered compliance period based on the size of the company. As noted elsewhere in our comments, we believe this rule, as proposed, is so economically burdensome that irrespective of a multi-year phase-in period, small businesses will not be able to meet the requirements and will be driven out of the market. Thus, a three-year phase-in period neither satisfies the small business impact assessment of this rule or the economic realities of the marketplace. A multi-year phase-in approach will be very confusing to consumers who will find it difficult to understand why only a portion of the dietary supplement industry meets quality standards, which FDA in its preamble states are necessary to assure public health and safety. Why then would not all companies be required to meet a regulation intended to protect public health? Moreover, suppliers, processors and handlers of dietary supplements will find it extraordinarily difficult to provide products which meet

the requirements of this rule for some customers but not all. In short, a three-year phase-in is impractical, confusing and unhelpful to small businesses as an attempt to help them "bridge" into new GMP regulations.

We recommend that a single compliance period and effective date be applied to all companies, which we believe should be three years. We would also support earlier "kick-in" requirements such as raw material testing or written standard operating procedures to help accelerate important GMP practices that provide the greatest benefit to industry and to consumers.

10. **Definition of Terms.**

Throughout this proposed rule, various terms are used but which are not clearly defined by the agency. We request that all terms of significance such as: lot, batch, component, identity, purity, quality, strength, composition, sanitize, etc., be defined and presented together for ease of convenience and avoidance of confusion.

An example of this is the lack of definition for the term "component" which could be interpreted to mean any constituent present in a botanical extract or other natural product. We understand "component" to mean an individual ingredient in a dietary supplement and not a constituent or substance within a dietary ingredient.

11. **Recognition of the American Herbal Pharmacopoeia as an Authoritative Source.**

Throughout Section 111.35, the agency outlines the applicability of numerous methods that can be utilized for the identification and quality assessment of botanical ingredients. These include macroscopic, microscopic and various types of chemical analyses. AOAC International and the United States Pharmacopoeia have been cited as "authoritative" sources for such methods. In addition, we have found the botanical monographs of the American Herbal Pharmacopoeia (AHP) to be among the most useful and scientifically credible sources of identification testing and quality control information for botanical ingredients. These monographs contain methods of identification for both the authentic material and potential adulterants as well as valuable information regarding sourcing of quality materials. We believe that the agency should explicitly acknowledge AHP monographs as an authoritative source of scientifically valid quality standards for botanical dietary ingredients and botanical dietary supplements.

12. **Good Agricultural Practices.**

We believe that Good Agricultural Practices (GAP) are a necessary and pertinent aspect of GMPs to enhance safety and conformity to specifications set for dietary ingredients. However, GAPs only apply to a sector of the dietary supplement industry and should be developed as part of a subset GMP for

botanicals and should be a component of the vendor management process established within this subset GMP.

SUMMARY

We appreciate this opportunity to provide comments on this regulation for dietary supplements good manufacturing practices. We offer our continued support and willingness to cooperate with FDA to develop final regulations that reflect economic realities and a high common standard for the manufacture and sale of high quality dietary supplements.

We would like reserve the right to provide additional comment as we get additional information from FDA and other sources.

Sincerely,

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