



September 9, 2003

1 14 20 1 21 2003

Dockets Management Branch (HFA-305)  
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 the Utah Natural Products Alliance (UNPA), a dietary supplement trade association representing many of the dietary supplement and ingredient suppliers from Utah and other states. The UNPA was actively involved in the development of the Dietary Supplement Health and Education Act (DSHEA), along with other interested parties and trade associations from our industry. UNPA remains actively involved in dietary supplement regulatory issues and is pleased to comment on FDA's regulation proposing good manufacturing practices for dietary supplements.

In this proposed rule, the agency published a very lengthy preamble detailing its rationale for this proposed regulation and requested comments on at least 86 specific points. The UNPA believes 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, the National Nutritional Foods Association and the American Herbal Products Association will be filing comments which will cover, in detail, many of the 86 specific points raised by the agency.

96N-0417

C245

UNPA COMMENT ON PROPOSED GMP, 03

## 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, the UNPA fully endorses the need for rigorous and adequate dietary supplement GMPs modeled on cGMPs for conventional foods. UNPA wishes to affirm its full support for the issuance of final GMP regulations, which will serve both the industry and its consumers.

The UNPA does 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. The agency also clearly states in this proposed rule that the detection and avoidance of adulteration is a principal feature in the construction of this proposed rule.

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.

UNPA 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, the UNPA does 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.**

The UNPA has carefully reviewed the economic analysis in the proposed rule as well as the underlying statistical data collected by FDA, which formed the basis of FDA's conclusions with regard to costs and benefits associated with this rule making. It is our conclusion that this data set is so fundamentally flawed that an entirely new analysis is required.

The agency calculated total benefits accruing from this proposed rule at \$260,620,604, broken out as follows:

- Reduction in illness: \$38,862,333
- Reduction in cost of recalling product: \$2,628,285
- Avoidance of catastrophic events: \$66,130,036
- Reduced search time by consumers: \$109,000,000

**TOTAL: \$216,620,654**

Costs to industry were calculated at a one-time cost of \$54,481,620 and an annual recurring cost of \$79,362,717.

In fact, costs to industry are far greater (we estimate at nearly \$1 billion), and benefits far lower (+/- \$30 million). We concur with the cost/benefit analysis submitted by the Council for Responsible Nutrition (CRN) as an accurate and comprehensive estimation of true costs and benefits associated with this proposed rule. We wish to associate ourselves with those comments.

We recognize the difficulty faced by the agency in collecting reliable data on which to base its economic analysis, a fact noted by the FDA as a significant limiting factor in arriving at reliable figures.

With respect to benefits of this rule, it is UNPA's view that the benefit of "reduced consumer search time" is an illusory benefit. Many dietary supplement consumers regard research, study and evaluation of product choices as an intrinsic part of the process of choosing, buying and using dietary supplements. Consumers do assess formulations, the natural and organic quality of ingredients, potency and price as factors in making their purchasing decisions. We do not believe consumers are able to assess the "quality" of a dietary supplement as a function of GMP compliance, and that no meaningful benefit accrues to consumers by a reduction in the thinking or selection process of such products.

This proposed rule places great emphasis on finished product testing as a principal tool to assure compliance with GMP regulations. This is both inappropriate and extraordinarily expensive. As stated elsewhere in our comments, it is impossible to "test" quality into any product, and finished product testing in particular places the emphasis at the wrong point of production. Moreover, Section 9 of DSHEA ("Good Manufacturing Practices")

clearly states that this regulation shall be modeled after current Good Manufacturing Practice regulations for food and **may not impose standards for which there is no current and generally available analytical methodology**. We believe this regulation as proposed does impose such a standard (finished product testing as the principal means of confirming conformance to GMP), and that there are no current and generally available analytical methods for many products subjected to this regulation. Finished product testing would require development of a significant number of new analytical methods in order to adequately determine strength, potency and purity of a complex matrix of ingredients bound up in excipients, binders, fillers, etc. A significant percentage of dietary supplements contain a blend of non-nutrient dietary ingredients such as botanicals, marine products, probiotics, etc. Currently, there are virtually no analytical methods available to test these products in finished form. Based on consultation with analytical laboratories and other experts in the field, we estimate that development of a single analytical method for a 10-ingredient, non-nutrient dietary supplement to be somewhere between \$50,000-100,000 – if it can be done at all. This expense, when added as a cost of production, would make small batch production economically unfeasible. This would cause virtually all small volume products to be discontinued by their manufacturers, as they would become economically unfeasible. For small business, this is all of their products. We believe the economic impact of FDA's proposed rule is disproportionately burdensome to small industry as they, by in large, do not have in-house testing capability and would be subjected to extraordinary capital costs to build an in-house laboratory or to bear the tremendous cost of outside testing.

We wish to point out that FDA's reference No. E51 states that the average cost of an analytical test would be \$60. Reference No. E51 refers to the 1999

published price list of Plant Bioactives, Inc., a Utah-based analytical laboratory. We have consulted with the owner and principal of Plant Bioactives, Inc., who has advised that the average test cost ranges between \$180-360 per test (see Attachment I).

UNPA believes the agency must reconsider not only its cost/benefit analysis but the entire premise on which this regulation has been developed.

We restate our firm commitment to supporting a rigorous and comprehensive Good Manufacturing Practice regulation for dietary supplements. This rule, unfortunately, imposes a drug-based GMP model that would bankrupt virtually all of small business and much of medium-sized business. Large business would suffer substantial losses of revenue and consumer goodwill as a result of significant price increases forced by the tremendous additional cost of testing imposed by this rule.

In consultation with the chief economist for the State of Utah, we estimate that for every 1% of retail price increase, a 1% reduction of consumer usage will occur. UNPA's membership estimates that the net increase to cost of goods will be between 9-13%, which will translate into an increased retail price of many products exceeding 20%. If the 1:1 price increase/loss to consumer ratio applies, our companies estimate a loss of sales revenue in the range of 20%.

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

The UNPA wishes to express its 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. The UNPA believes 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.

UNPA is 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. There is no precedent for this requirement under cGMPs for foods. (See comment under Section I above.) Moreover, UNPA believes 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. UNPA objects 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.

## **CASE STUDY I**

*Assumptions:* Based on in-house costs of testing for a large business with experience and trained staff and efficiencies in volume testing of products.

Average ingredients per product:	16
Required finished product tests per year (all components x all batches x one test per component):	15,000
Average cost per test:	\$150
Additional cost of finished product testing (per year):	\$2.25 million
Increase to cost of goods:	20%
Estimated increase in annual cost of raw materials by suppliers required to test all of their finished raw materials:	\$7-10 million

## **CASE STUDY II**

(The figures below relate to vitamin/mineral products only)

Average ingredients per product	36
Required finished product tests per year (all components x all batches x one test per component):	30,240
Average cost per test:	\$150
Additional cost of finished product testing (per year):	\$4.5 million
Increase to cost of goods:	12%
Estimated increase in annual cost of raw materials by suppliers required to test all of their finished raw materials:	\$7.37 million

In both cases, these companies are well-established businesses with competent staff and significant internal scientific expertise.

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.

We believe that FDA has underestimated the cost of testing for finished and raw materials by a multiple of at least 3 to 6 times. 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. 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 and therefore respectfully request additional time to submit our updated economic analysis and effect on small business when it is completed.

## **8. Certified Vendor Programs.**

UNPA strongly believes 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). UNPA believes 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.**

UNPA believes 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.

### **13. Practitioner and Educational Use Exemption.**

A growing number of clinicians, practitioners and academics recommend and/or dispense dietary supplements to their clients or patients. Often, such practitioners purchase finished raw materials to blend or formulate products using simple techniques or processes. Such products are typically custom-blended and provided to the patient or user under professional supervision. Such practitioners are essentially non-commercial enterprises and are thus not in a position to absorb the costs or the requirements intended to be applied to businesses which manufacture or process dietary supplements for interstate commercial sale. Accordingly, UNPA believes that such practitioners, clinicians and educators should be exempt from the final rule to assure continued access of specially formulated/blended dietary supplement formulas to their patients.

### **SUMMARY**

The UNPA appreciates 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.

Sincerely,

UTAH NATURAL PRODUCTS ALLIANCE



Loren Israelson  
Executive Director

/hhc