Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fisher Lane, rm. 1061
Rockville, MD 20852
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Docket No. 96N-0417

To Whom It May Concern:

We at 4Life Research both manufacture and distribute dietary supplements. We are submitting these comments to the 'Proposed Rule for Current Good Manufacturing Practice for Dietary Supplements' (Docket No. 96N-0417). We have participated with the working groups of both Utah Natural Product Alliance (UNPA) and the American Herbal Products Association (AHPA) that represent our industry. It has come to our attention that some information relating to the economic impact of the proposed rule was omitted from the publication and we reserve the right to submit additional comments.

We have received comments from other associations in the industry such as CRN, NNFA, and AHP and note that they raise and share many of the same concerns that we have. It has been alleged that the pharmaceutical manufactures of vitamins, if required to adhere to these proposed GMPs, may refuse to sell to the DS industry. These companies already comply with drug cGMPs but would apparently opt out rather than try to comply with the proposed requirements of these proposed GMPs, a good indication that these proposed rules have strayed from what congress intended when DSHEA was enacted.

Our comments to the proposed GMP rules are as follows:

1. <u>Legal Authority to Issue these proposed GMP Rules.</u>

With respect to FDA's request for comments on the agency's legal authority to issue this regulation, 4Life Research fully endorses the need for rigorous and adequate dietary supplement GMPs modeled on cGMPs for conventional foods. 4Life Research wishes to affirm its full support for the issuance of final GMP regulations, which will serve both the industry and its consumers.

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4Life Research 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.

4Life Research 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. 4Life Research does not believe that the agency has the legal authority to issue a final regulation for dietary supplement GMPs that include in material or significant ways provisions from drug, medical device or other GMPs. It was plainly understood by us in the industry that the statement 'modeled after food GMPs regulations' meant they were to be food like GMPs not drug like GMPs, and the authors have misrepresented the meaning of modeled.

It is our view along with many others in the industry with whom we have met that the authors of the proposed rule have exceeded the statutory authority granted to them by congress, which has now encumbered the process of getting into place GMPs that are food not drug like that the dietary supplement industry desires. Because the authors exceed the mandate the proposal they have made is so misaligned that it makes it extremely difficult to comment on sections that should, we believe, never have appeared in the proposed rule. And, in other cases significant omissions such as subset to the GMS that should have been included. Consequently, it would seem prudent for the agency in cooperation with industry representatives to rewrite many of the sections followed by requesting additional comments from the industry.

2. Testing of Raw Materials & Finished Products and the Economic Impact on our Company and Others in the Industry.

4Life Research has concluded 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 lacked 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. 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. 4Life Research is actively collecting additional data to assess, more accurately, costs associated with raw material and finished product testing, and again requests the opportunity to present additional data within 30 days after the comment period closes. We underscore our view that 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 as the appropriate means to assure product quality, purity and safety.

3. Failure to Adequately and Clearly Define Important 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 and every constituent present in a botanical extract or other natural product. Of course during the last 100 years natural product chemists have not identified all of the constituents of a single botanical, which indicates how impractical it would be to require us to establish methods for all of the botanicals we currently use.

In response to your request to comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements we note the following:

Within the proposed GMPs are repeated requirements testing for `identity, purity, quality, strength, and composition' throughout the manufacturing process. On page 12176 these terms are given the following meaning: 'The phrase "identity, purity, quality, strength, and composition," means 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 for its intended purpose (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 phrase 'without impurities' should be changed to 'of limited impurities', since in scientific terms 'without impurities' is an impossible standard.)

One obvious interpretation of the term 'component', which by the definition includes 'product-related substances', is every component or substance in each botanical in a product. On page 12252 'component' is given the following meaning 'Component means any substance intended for use in the manufacture of a dietary ingredient or dietary supplement including those that may not appear in the finished dietary ingredient or dietary supplement. Component includes

ingredients and dietary ingredients as described in section 201(ff) of the Act. Included in the definition in section 201(ff) are every 'metabolite, constituent' of an herb or other botanical'.

As written these proposed GMPs require triplicate testing of every constituent and metabolite of every botanical in a particular product. Since a single botanical can contain tens of thousands of constituents and metabolites, analytical costs would quickly escalate into millions of dollars for each lot, and this for a product whose total annual revenues would be less than the testing costs.

These costs render the economic impact statements given in the proposal grossly deficient. It would not put '350 companies' out of business as the agency suggests, rather it would put every cGMP compliant company in the industry out of business.

Given the statement on page 12197 'We recognize that certain tests for identity, purity, quality, strength, or composition for certain finished product may not be available due to complex finished matrices that would make such testing impracticable' one must also conclude that even the scientifically practical tests are economically prohibitive because of the thousands of test that are required.

If some other conclusion concerning 'components, constituents and metabolites' than that given above was intended by the authors then they should have so stated.

We recommend that the term 'strength' be replaced with the term 'quantity' to be expressed in wt/wt%, volume%, IU, or other applicable units. The term 'composition' should be removed from the proposed rule.

4. <u>FDA's Explanation and Rationale for this Proposed Rule – Protection of Public Health</u>.

4Life Research wishes to express its surprise and concern with respect to the reasons of public health as 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.

5. 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 products, marine products, probiotics and other substances. These materials also range from synthetic fine bulk chemicals to complex plant extracts. The complexity, expertise, available analytical methods and production requirements and associated expenses to assure consistent quality and safety for these various materials are profoundly different. 4Life Research believes the agency should take these differences into account by developing, in cooperation with industry, subset GMPs for those dietary supplement categories (vitamins and minerals, botanicals, colostrums, fermented or live culture product, animal tissue, and others) 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 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 subset requirements that serve to assure the safety, potency and purity of widely diversified DS products.

6. <u>All Dietary and Other Ingredients Must be Lawfully Sold</u>.

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

5. Authorized for use as a food additive;
6. Authorized by prior sanction;
7. 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.

4Life Research 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 such as excipients 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.

Section 4 of the DSHEA 'Safety of Dietary Supplements and Burden of Proof on FDA' we believe should not be materially contradicted in cGMPs for dietary supplements, particularly as it pertains to commonly used ingredients such as grandfathered botanicals, excipients, and items with a long history of human use.

7. 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, 4Life Research 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.

8. 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. 4Life Research objects to this proposal on four 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. Botanicals often contain common constituents such as polyphenols. When these botanicals are combined to make a finished product final testing cannot determine from which botanical they came. Were as in raw material testing of a single ingredient the results can be determined.
- An inspector could readily conclude that the term composition refers to every constituent of every botanical (see item 3 above). There are hundreds of existing tests that are possible to perform on thousands of botanical constituents but that would be economically exhausting and would not contribute to quality or safety. Again, we propose that the term be dropped from the proposed rule.

The testing requirements of the proposed GMPs would result in testing costs that our company could not financially withstand. We could and would sustain testing cost of GMPs that are food like.

If in the limited sense of the proposed GMPs we test for each ingredient listed on the label and for constituents listed on the label (example ginkgo biloba leaf (7% terpene lactones) where ginkgo biloba is the ingredient and terpene lactones are the constituents (wt/wt%). And, in

addition ingredient and claimed constituent testing if we perform micro, heavy metals, limited pesticide testing the cost to us would be as follows:

TESTING:

Total combined yeast and mold count - **$15**	Covance Laboratories Inc. - January 2002
Heavy Metal analysis - **$262** Lead, Arsenic, Mercury	Covance Laboratories Inc. - January 2002
Pesticide analysis – average **$247**	Covance Laboratories Inc. - January 2002
Microorganism analysis – **$177** *Salmonella, E. Coli, Staphylococcus aureus & Aerobic microbial count*	Covance Laboratories Inc. - January 2002
Identity, and Quantity analysis Average Each Ingredient - **$108**	Covance Laboratories Inc. January 2002 Plant Bioactives Research Inst. June 2003

ANALYSIS:

The average number of ingredients in each product is:	**36**
Min. cost for single production of 7 products: (Number of ingredients x number of identity and quantity analyses x number of products + cost for other contaminant tests)	**$27,917***
Batches produced annually:	**120**
Annual additional cost to produce 7 products: (27,917 x the 3 minimum times each ingredient must be tested for in the production process x number of batches annually)	**$10 million**
Equipment for Analysis Lab:	**$1.5 – 2 million**

*Testing all components of each herb would result in exponentially higher costs than the above estimates. (40% of our ingredients are herbs.)

ESTIMATES:

Our Estimated Annual Expense of new GMPs:	**$11,500,000**
FDA Figures for Estimating the Same:	**$83,000**
Estimated Expenditure imposed as % of Annual Revenue	**19%**
Loss of sales due to necessary product price increase: *An increased price of 8% results in an 11% loss of customer sales.	**26%***

Since our profit after taxes is 4 to 6%, we cannot absorb a 19% cost increase we would incur. By passing on the costs to the consumer we would loose an estimated 26% of our customers, and it is very questionable that we would be able with remain in business with such losses. Of a certainty we would loose many of our employees.

These costs do not reflect the additional cost purchasing, laboratory space and personnel if testing were to be all done in house.

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.

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.

9. <u>Certified Vendor Programs</u>.

4Life Research strongly believes that the most effective means to assure that DS/DI conform to specifications for identity, quality, and quantity 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 programs, 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 the FDA requested comment on whether this proposed regulation should apply to foreign manufacturers of dietary ingredients and dietary supplements (DI/DS). 4Life Research 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.

10. <u>Implementation</u>.

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, businesses small and large 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.

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 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 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.

4Life Research 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.

SUMMARY

4Life Research 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 effective cGMPs and sale of high quality dietary supplements.

Finally, we recommend that the agency consider USDA to write and have jurisdiction of GMPs for Dietary Supplements. In the State of Utah the Department of Agriculture currently inspects for GMP compliance.