DOCUMENTS MANAGEMENT BRANCH (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

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Re: Proposed Rules on Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements, Docket No 95N-0417

COMMENTS OF
NATURE'S SUNSHINE PRODUCTS, INC. PROVO, UTAH 84606

Nature's Sunshine Products, Inc. manufactures and markets a wide variety of herbal-based dietary supplements. Many of these products are affected by the above referenced proposed regulations. Therefore, NSP and its members are interested in these proposals and offer the following comments in respect to them.

Background and Summary

The Dietary Supplement Health and Education Act of 1994 (DSHEA), signed into law on October 25, 1994, provides that the Secretary of Health and Human Services may prescribe current good manufacturing practice (CGMP) regulations for foods: and that any such CGMP not impose standards for which there is no current and generally available analytical methodology.

AHPA, in association with other industry trade groups, submitted a proposal for CGMP regulations for dietary supplements (the Industry Draft) to the Food and Drug Administration proposed rulemaking (ANPR). The Industry Draft was published by FDA in the Federal Register on February 6, 1997 The ANPR is the subject of these comments.

FDA requests comments on whether it should institute rulemaking to develop CGMP regulations for dietary supplements and dietary supplement ingredients, and, if it should, what constitutes CGMP for these products. NSP believes that FDA should institute such rulemaking and that the Industry Draft constitutes the appropriate CGMP regulations for dietary supplements and ingredients thereof.

The primary focus of the balance of these comments is on Section IV (summary and request for Comments) of the ANPR. Generally, our comments are taken from the "Comments of the American Herbal Products Association" and are repeated herein for emphasis and for showing NSP is indeed in accordance with the American Herbal Products Association Comments as well as with the Industry Draft.

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Comments to Section IV: Summary and Request for Comments

1. Defect Action Levels

FDA is questioning whether there is a need to establish Defect Action Levels (DALs) for dietary supplements.

The Food and Drug Administration defines DALs as natural or unavoidable defects for human use that present no health hazard.

Botanicals are generally wild crafted, sun-dried raw agricultural commodities grown, harvested and distributed under rather primitive conditions. Quite often, handling and initial processing of botanicals in exporting countries are performed outdoors on small family farms where they are exposed to birds, rodents, insects, etc. Spices, on the other hand, are usually cultivated under controlled conditions. Consequently, spices in comparison might contain fewer unavoidable contaminants.

DALs are established because it is not possible to grow in open fields, harvest, and process crops that are totally free of natural defects. In addition, botanicals that are wild crafted are not subject to pesticide applications which would enhance the possibility of pest contamination.

Considering the above discussion, dietary supplements industry especially the botanical side of our industry might face a rather difficult if not impossible task to comply with any established DALs which are not based on actual data.

American Herbal Product association (AHPA) is therefore undertaking the data collection process toward the establishment of DALs for certain high volume herbs. The compilation will be accomplished by providing samples from AHPA member companies to a third party laboratory with extensive experience on DALs determination, where analysis will be performed to determine the actual levels of defects found in these herbs. The raw data can be submitted to FDA for the established of DALs on botanicals.

2. Testing Requirements for Ingredient Identification

Industry submission:
(c. 7. iv.) "Each lot of raw material shall undergo at least one test by the manufacturer to verify its identity. Such tests may include any appropriate test with sufficient to determine identity, including chemical and laboratory tests, gross organoleptic analysis, microscopic identification, or analysis of constituent markers."

FDA issue:
"FDA requests comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements." "FDA is asking for comments on the technical and scientific feasibility for the identification of different types of dietary ingredients."
Reply:
In the assurance of the identity of plant materials, there are two important aspects to consider. The first is the identity of the plant material, i.e. determination of the correct Latin binomial name and the second is assurance of the presence of chemical constants appropriate for that plant material. It may be appropriate for the supplier of the raw material to verify the identity of the plant material and for the manufacturer to verify the presence of appropriate constituent chemicals.

The primary way to identify plant material is through the use of voucher specimens. (These are preserved specimens that include as many parts of the plant as possible, including the stem, leaves, flowers, seeds and roots. The plant material is pressed flat, dried and placed on a 11 1/2" by 16 1/2" card. Specimens are identified by a trained botanist with the aid of published descriptions and comparisons with previously identified specimens.) As the whole plant is needed, this form of identification is most appropriate for the primary supplier of the plant material, i.e. the farm or the wildcrafter. It would be appropriate for a "Certificate of Botanical Identity" to be produced at this point and for this "Certificate" to follow the material through the manufacturing process forming a paper trail. Thus the identity of the plant material could be traced through all stages of processing to the final consumer product. Any questions of identity could be addressed through examination of the voucher specimen which would be held for a specified period of time or if necessary serve as a permanent record.

In the absence of a voucher specimen there are other means of identification of plant material that are covered in monographs specific to the plant. General descriptions as to appearance or sensory (organoleptic) information can be very useful to those experienced with plant materials. Milled or powdered plant material can be identified using microscopic analysis, although there are not many people trained with the expertise to do so. Simple chemical spot tests are indicative of identity but are not definitive. Verification of the presence of chemical constituents is important, especially for processed materials. These can include simple chemical spot tests for classes of chemicals or determination of presence of essential oil content which can be easily set up. More sophisticated analysis such as chromatographic techniques (thin layer (TLC,

HPTLC), high pressure liquid (HPLC), gas (GC), capillary electrophoresis (CE) and spectroscopic analysis infra-red (IR, FTIR), and mass spectrometry (MS)) are more definitive but may cause economic hardship to smaller manufacturers. As official monographs are developed and approved, standardized analytical methodology for identity, quality and composition will be provided for the industry.

Proposed revision:
Each lot of raw material shall undergo at least one test by the manufacturer to verify its identity. In the case of plant material, the identification method performed shall be applicable to the state of the plant material, including but not limited to voucher specimens, microscopic analysis and organoleptic examination. A certificate of botanical identity provided by the raw material supplier shall qualify as verification of the identity of processed or manufactured material. Processed or manufactured material shall be analyzed for the presence of chemical constituents. Such test may include but not limited to chemical spot tests, assays or essential oil content, chromatographic assays such as thin layer (TLC, HPTLC), high pressure liquid (HPLC), gas (GC), capillary electrophoresis (CE) and spectroscopic analysis such as infra-red (IR, FTIR).

3. Contamination, Quality and Identification Criteria

FDA requests comments on standards that should be met in certifying that a dietary ingredient or dietary supplement is not contaminated with filth, pesticide residues, or other harmful contaminants or other impurities; that it is microbiologically safe; and that it meets specified quality and identity standards.

As noted in the ANPR, it is a CGMP for food for a manufacturer to accept certification from suppliers that ingredients are free from such adulteration as is described above. DSHEA specifies that any CGMP regulations prescribed for dietary supplement shall be modeled after CGMP regulations for food; therefore, NSP believes that, in order to satisfy DSHEA's requirement for any prescribed CGMP regulations for dietary supplements, certification from suppliers regarding the adulteration issues described here must be defined as acceptable, provided that the manufacturer of the dietary supplement establishes the reliability of the suppliers examination or analysis.

FDA erroneously states that many ingredients used in dietary supplements do not have a history of food use in the United States, and so stating questions the validity of suppliers certification with regard to both identity and adulteration. In fact, almost all of the dietary ingredients used in dietary supplements were marketed in the United States before October 15, 1994. Any dietary ingredient that was not marketed in the United States before October 15, 1994 is defined by the DSHEA as a "new dietary ingredient", and is subject to specific requirements to attest to its safety. If FDA is aware of specific new dietary ingredients which are not in conformity with the statutory requirements for such ingredients, NSP strongly supports the agency in its use of its regulatory authority to control such illegal actions.

On the other hand, DSHEA specifically acknowledges that dietary supplements are "safe within a broad range of intake", and that "safety problems with the supplements are relatively rare". Industry has continually monitored records from the Center for Disease Control, Poison Control Centers, and the FDA and can find no substantial historical or contemporary data which contradicts the record of safe consumption of dietary supplements which is noted in DSHEA. It must be assumed that this safe consumption record is for dietary supplements have always been subject to CGMP regulations for food, since dietary supplements have always been subject CGMP regulations for food. NSP therefore believes that it is neither necessary nor appropriate to subject dietary supplements to a more stringent requirement that the certification that is mandated for foods in order to assure that dietary supplements are free from adulteration, provided that the manufacturers of the dietary supplements establishes the reliability of the suppliers certification.

In conclusion, NSP believes that the agency's concern which is the subject of this specific request for comments is fully addressed in the Industry Draft in the section titled Production and Process Controls, subsection (c), numbers (1) through (7). Furthermore, NSP believes that a manufacturer's acceptance of certification from suppliers that dietary ingredients and dietary supplements are free from such adulteration as is described above is an appropriate standard for certifying that dietary ingredients and dietary supplements are, in fact, free from supplement establishes the reliability of the suppliers examination or analysis.

4. Documentation Procedures

The agency asks for comments on whether there is a need for CGMP to include requirements for manufacturers to establish procedures to document that the procedures prescribed for the manufacturer of a dietary supplement are followed on a continuing or day-to-day basis. The agency also acknowledges that no provision of part 110 (CGMP regulations for foods) requires such documentation.

DSHEA specifically states that any CGMP regulations prescribed for dietary supplements be modeled after CGMP regulations for food. One of the most significant differences between CGMP regulations for food and those prescribed for drugs is the requirement for manufacturers of drugs to document that the procedures prescribed for the manufacture of a drug are followed. NSP believes that such documentation is not necessary to ensure that dietary supplements are safe for their intended use, and that the agency would be ignoring the statute's intent in this regard if it were to require such documentation.

As stated in response to the previous request for comments ("3. Contamination, Quality and Identification Criteria"), both DSHEA and historical data substantiate the general safety associated with the consumption of dietary supplements. NSP does not believe

that CGMP regulations which are appropriate for drugs are required to ensure that this established safe consumption history be maintained.

The agency states that its tentative judgment is that section 402(g) of the Federal Food Drug and Cosmetic Act, which states that any CGMP regulations for dietary supplements be modeled after the CGMP regulations for food, does not preclude FDA from adopting CGMP regulations for dietary supplements that have no counterpart in part 110 (21 CFR 110) if there is an appropriate basis for doing so. NSP disagrees with this judgment, and believes that the words "modeled after current good manufacturing regulations for food" only meaning within the context of part 110, and that part's definitions and regulations.

5. Adverse Event Reporting

The agency asks for comments on whether dietary supplement CGMP should require the establishment of procedures to determine whether an injury or illness reported by a consumer of a dietary supplement constitutes a serious problem and whether any such procedure should require evaluation by competent medical authorities rather than quality control or nonmedical scientific/regulatory personnel. The agency provides as its rationale for requesting these comments the supposition that many dietary supplements may contain pharmacologically active substances, that some may contain potential allergen that result in adverse events in certain consumers, and that there is potential for serious injury or illness in some persons from the consumption of such substances.

As stated in response to the two previous requests for comments ("3. Contamination, Quality and Identification Criteria"; and "4. Documentation Procedures"), both DSHEA and historical data substantiate the general safety associated with the consumption of dietary supplements. Furthermore, the concerns which the agency provides as its rationale for requesting comments on the establishment of special adverse event reporting requirements for dietary supplements are equally as relevant to food as to dietary supplements. The vitamin C in an orange is no less pharmacologically active as an ingredient in a carbonated beverage food than as an ingredient in a dietary supplement. The potential and actual allergic response to many food is well known, as is the serious injury or illness in some persons from the consumption of such foods as peanuts. It must be assumed that the agency believes that the current CGMP regulations for food are sufficient to protect the public health, although CGMP regulations for food do not require the establishment of procedures to determine whether an injury or illness reported by a consumer of a food constitutes a serious problem and do not require evaluation of such reports by competent medical authorities rather than quality control or nonmedical scientific/regulatory personnel.

For reasons stated above, that is, that safety problems associated with dietary supplements are relatively rare, and that CGMP regulations for food are sufficient to protect the public health, NSP does not believe that CGMP regulations which would require adverse event evaluation or reporting for dietary supplements which is different for that required for food is necessary to protect the public health.

6. Safety Evaluation of Dietary Ingredients

The agency asks for comments on whether CGMP for dietary supplements should require that manufactures establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients, whether a manufacturer should be required to perform an evaluation of the available scientific information on the safety of dietary ingredients that it intends to use in its products to assure that those products will be safe, and, if so, whether and in what manner records of such evaluation should be documented. The agency gives as its rational for requesting these comments its belief that many dietary ingredients have little history of use in food in the United States or of use in the amounts that would be used in a dietary supplement, and the fact that DSHEA has specifically excepted dietary supplements from the definition of "food additive".

NSP believes that FDA is incorrect in its statement that many dietary ingredients have little history of use in food in the United States before October 15, 1994. An dietary ingredient that was not marketed in the United States before October 15, 1994 is defined by DSHEA as a "new dietary ingredient", and is subject specific requirements for such ingredients, NSP strongly supports the agency in its use of its regulatory authority to control such illegal actions.

NSP also believes that FDA is incorrect in its statement that many dietary ingredients have little history of use in the amounts that would be used in a dietary supplement. In fact, the existence of dietary supplements already in the marketplace is well known to the agency, and was well known to Congress at the time of the passage of DSHEA. As has been stated above in response to three previous requests for comments ("3. Contamination, Quality and Identification Criteria"; "4. Documentation Procedures"; "5. Adverse Event Reporting"), both DSHEA and historical data substantiate the general safety associated with the consumption of dietary supplements. Presumably this safe usage history is related to the amount of dietary ingredients historically used in dietary supplements.

NSP does not understand how the agency's mention of the exception of dietary ingredients from the definition of "food additive" is in any way relevant to this specific comment is based on the definition of "food additive" or the exception of dietary supplements from this definition.

In conclusion, NSP believes that the agency's concern which is the subject of this specific request for comments is fully addressed in the Industry Draft in the section titled *Production and Process Controls,* and especially in subsection (d) and (e).

7. Controls for Computer Assisted Operations.

FDA is requesting comments on how best to ensure that software and equipment used to direct and monitor the manufacturing process are properly....validated and monitored.

The software and or equipment has to be tested and validated against manual operations or tests for each separate product that the manufacturing process produces using the software or test equipment. The results must correlate within a certain degree of confidence and be duplicable by independent personnel. The validation procedures and results must be documented and the records should be trained for at least one year after the expiration date of the batch. If the expiration date is not identified on the product, the validation procedure and results must be documented and the records should be retained for at least three years after the date of manufacture.

8. Relevance of HACCP

FDA is asking if Hazard Analysis and Critical Control Point (HACCP), rather than Proposed CGMP, may more effectively address the requirements of manufacturing and handling dietary products.

Subjecting the dietary supplement industry to HACCP and requirements will represent a major change in our processing, distributing and retailing approach. NSP opposes the mandating of HACCP and legislative or administrative action. Record keeping and actual implementation of the HACCP principles should not be mandated, but whether these activities should remain within the responsibility of the manufacturer, distributor, or retailer of dietary supplements.

The HACCP program should be mandated for only the high risk products such as fresh meat, poultry and seafood. The dietary supplement products which impose little or no safety risk, should not be burdened by the elaborate HACCP requirements much beyond the GMP scope. NSP has implemented the HACCP principles in our operation. We strongly believe that the establishment of HACCP makes good business sense. HACCP is the best preventive measure to insure the safety of the dietary supplements. The FDA, the academia and the industry may work together to develop the principle that should be implemented. The FDA's involvement should be in research, education and design of the proper training procedures rather than bureaucratic enforcement.

Respectfully submitted,

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