Re: Proposed Rules on Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements, Docket No. 96N-0417

COMMENTS OF THE AMERICAN HERBAL PRODUCTS ASSOCIATION

The American Herbal Products Association (AHPA) is a trade association of companies involved in the manufacture and marketing of food products and dietary supplements containing herbal ingredients. Many of these products are affected by the above referenced proposed regulations. Therefore AHPA 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 dietary supplements; that any such CGMP be modeled after 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 (FDA), November 1995. The Industry Draft was included in the Advanced Notice of Proposed Rulemaking (ANPR) 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 regulations for these products. AHPA reiterates here its belief, implicit in its involvement with other industry trade groups in developing the Industry Draft, that FDA should institute such rulemaking and that the Industry Draft constitutes the appropriate CGMP regulations for dietary supplements and ingredients thereof, with the following modifications:

1) AHPA is aware of and support the specific amendments to the Draft provision detailed in the comment on these ANPR submitted by the Council for Responsible Nutrition.

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2) The *Exclusions* section should be stated as:

The following operations are not subject to this part: Establishments engaged solely in the harvesting, dehydrating, storage, or distribution of one or more raw and or dehydrated agricultural commodities which are ordinarily cleaned, prepared, treated, or otherwise processed before being marketed to the consuming public. Also excluded are establishments engaged in the harvesting, dehydrating, handling, processing, manufacturing, storage, or distribution of raw and processed agricultural commodities including but not limited to culinary herbs, spices and dehydrated vegetables which are not sold as dietary ingredients or dietary supplements.

3) The following language in to Subparagraph (c) (7) (iv) of the section entitled *Production and Process Controls* in the Industry Draft rewritten to read: In lieu of such testing by the manufacturer, a certificate of analysis may be accepted from the supplier of the raw material provided that the manufacturer establishes the reliability of the supplier's identification.

ADD THE FOLLOWING:
Identification of botanical raw materials shall be determined on unprocessed plant material. Such identification may be based on macroscopic or microscopic taxonomic features, the use of voucher specimens, or any other appropriate method to assure identification. Raw material suppliers who are subject to these CGMP regulations shall state the botanical identity on a certificate of analysis.

In responding to certain of the agency's requests for comments, it is important to be aware of the fact that many of the products which are now defined as dietary ingredients and dietary supplements were already being consumed prior to the passage of DSHEA. In the specific requests numbered "3" and "6", FDA states that many dietary ingredients do not have a history of food use 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 DSHEA as a "new dietary ingredient", and is subject to specific requirements to attest to its safety.

AHPA also believes that FDA, as is evident from the rationale presented by the agency in the specific requests for comments numbered "1", "5" and "6", is not aware of the history of safe use of dietary supplements. In each of these specific requests the agency states a particular safety concern, either based on the fact that the amount of a dietary ingredient used in a dietary supplement is greater than the amount that would be consumed when the same ingredient is used as a food, or on the statement that some dietary ingredients are pharmacologically active or may contain potential allergens. 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 continued to monitor 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 that is noted in DSHEA.

In two specific requests for comments (numbered "4" and "5"), FDA states its tentative judgment 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. AHPA strongly disagrees with this judgment and believes that the words "modeled after current good manufacturing regulations for food" only has meaning within the context of part 110, and that part's definitions and regulations. The guidelines presented in DSHEA for the development of CGMP regulations for dietary supplements is quite specific and must be honored.

AHPA also submits that dietary supplement regulations and the development of concurrent industry guidelines should follow historical models for the development of similar food regulations and industry guidelines. Historically, the food industry, such as the spice industry, has been allowed and encouraged to develop voluntary guidelines for specific product and process issues. FDA has often later adopted these guidelines as regulations or recommendations after industry has demonstrated their appropriateness empirically. A similar approach relying on industry experience and the co-development of methods which recognize the unique economics and usefulness of the dietary supplement industry will yield the best result for all parties.

The primary focus of the balance of these comments is on Section III (Economic Issues) and Section IV (Summary and Request for Comments) of the ANPR.

Comments to Section III: Economic Issues

The agency seeks information on how closely current practices in the dietary supplement industry conform to the Industry Draft and how costly it would be to bring established practices into conformity. The agency requests comments on whether CGMP regulations should be mandatory, and, if so, how long it would take establishments to come into compliance. The agency also requests comments on the effect of CGMP regulations on small businesses.

It must be recognized that the dietary supplement industry is comprised of a large variety of companies of all sizes. Smaller manufacturers have historically been the foundation of the industry; at the same time, there are a number of very large companies involved in the industry. It is this mix that has developed the favorable record of safety and consumer value recognized by Congress in their adoption of DSHEA.

As might be expected with such a broad range of sizes, AHPA believes that there is no single answer to the requested information. Certain of our members, especially the largest manufacturers and suppliers, have instituted GMPs which go far beyond those required for

foods. These are therefore less likely to suffer costly transition expenses. As the agency has stated and as we agree, instituting CGMP regulations for the industry has the potential to affect a significant number of small businesses. We are not able, however, to estimate such expense.

As stated earlier in these Comments, AHPA believes that the Industry Draft constitutes the appropriate CGMP regulations for dietary supplements. It was the intention of the broad industry coalition that developed the Draft to clarify those portions of the regulations that are meant to be mandatory by use of language which implies required conformity, i.e., the word "shall". In sections deemed to be voluntary, the word "should" was used.

With regard to estimating the time required to come into conformity with all mandated sections, it is again assumed that smaller companies might have to make more significant changes from current practices than larger companies. AHPA estimates that, if smaller companies were given 2 additional years beyond that allowed to large companies, mandated CGMP regulations could be instituted industry wide in a manner that is affordable to all companies.

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 ingredients and tentatively concludes that it would not be appropriate to apply the current DAL's to dietary supplements. The agency requests comments that would assist in developing DAL's for dietary supplements.

DAL's are described as natural or unavoidable defects in food for human use that present no health hazard (21CFR 110.110). The Industry Draft includes language adopted from CGMP regulations for foods authorizing the establishment of DAL's for dietary products whenever it is necessary and feasible to do so.

AHPA agrees with the agency's tentative conclusion that it would not be appropriate to apply current DAL's to dietary supplements. Furthermore, AHPA believes that the establishment of DAL's for dietary ingredients should be addressed in a separate procedure from the process of developing CGMP regulations for dietary supplements. Any DAL's for dietary ingredients, whether or not these are current DAL's established for foods, must be determined based on actual data from the specific ingredient as it appears in trade. This concept requires that the agency and industry work closely together to establish meaningful DAL's for dietary ingredients, and is consistent with the precedent established in the development of DAL's for food products, such as spices.

2. Testing Requirements for Ingredient Identification

FDA requests comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements. The agency also requests comments on the technical and scientific feasibility for the identification of different types of dietary ingredients, and solicits information on what constitutes "adequate testing" for identity of different types of ingredients and on effective alternatives to testing. AHPA's response to these requests for comments is limited to their relevance to plant materials used in dietary supplements.

The issue of positive identification of plants depends to a large degree on the form in which the plant enters into the manufacturing process. Unprocessed plants and plant parts (flowers, roots, leaves, etc.) can be readily analyzed by qualified and experienced personnel based on documented physical and morphological characteristics. This constitutes adequate testing for identity for unprocessed plant material. So long as precise record keeping of the identity of the plant material is initiated at this point, no additional analysis for identification should be required.

Upon milling, morphological characteristics are generally lost. Organoleptic factors, such as taste, smell, color, etc., may provide adequate information for identification or it may become necessary to use microscopic identification, chemical or laboratory tests, or analysis of marker constituents. However, we must reiterate that, with regard to the issue of identification, none of these types of analyses are required to adequately test any plant material which is properly identified in its unprocessed form, so long as accurate record keeping is maintained.

In conclusion then, AHPA believes that appropriate testing requirements for plant materials used in dietary supplements is well stated in the Industry Draft as modified by the language proposed to be added to Subparagraph (c) (7) (iv) of the section entitled *Production and Process Controls*, as stated on page 2 of these Comments.

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.

DSHEA specifies that any CGMP regulations prescribed for dietary supplements shall be modeled after CGMP regulations for food; therefore, AHPA believes that, in order to satisfy DSHEA's requirement for any prescribed CGMP regulations for dietary supplements, certification from suppliers must be defined as acceptable, provided that the manufacturer of the dietary supplements establishes the reliability of the supplier's 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 in so stating questions the validity of suppliers certification with regard to identity. 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 DSHEA as a "new dietary ingredient", and is subject to specific requirements to attest to its safety.

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". It must be assumed that this safe consumption record is for dietary supplements which are manufactured according to CGMP regulations for food, since dietary supplements have always been subject to CGMP regulations for food. AHPA therefore believes that it is neither necessary nor appropriate to subject dietary supplements to a more stringent requirement than the certification commonly used for foods provided that the manufacturers of the dietary supplements establishes the reliability of the suppliers certification.

In conclusion, AHPA 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).

4. Documentation Procedures

The agency asks for comments on whether there is a need for CGMP regulations to include requirements for manufacturers to establish procedures to document that the procedures prescribed for the manufacture 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 manufactures of drugs to document that the procedures prescribed for the manufacture of a drug are followed. AHPA 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. AHPA 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. AHPA strongly disagrees with this judgment, and believes that the words "modeled after current good manufacturing regulations for food" only has 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 non-medical scientific/regulatory personnel. The agency provides as its rationale for requesting these comments the supposition that many dietary supplements 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 than that in a dietary supplement tablet; guarana' 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 foods is well known, as is the serious injury or illness in some persons from the consumption of such foods as sesame seeds. (James, C., A. Williams-Akita, Y.A. K. Rao, L.T. Chiamonte, and A.T. Scheider. 1991. Sesame seed anaphylaxis. *New York State Journal of Medicine*. Oct: 457-458). 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 non-medical scientific/regulatory personnel.

For the 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, AHPA does not believe that the establishment of the procedures described in this request for comments is necessary to protect the public health.

6. Safety Evaluation of Dietary Ingredients

The agency asks for comments on whether CGMP regulations 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".

As stated in our response to FDAs 3rd request for comments("Contamination, Quality and Identification Criteria"), almost all of the dietary ingredients used in dietary supplements were marketed in the United States before October 15, 1994. Further, such use both in the United States and elsewhere in the world is well documented for the large majority of dietary supplements, and especially those representing the vast majority of actual sales.

AHPA 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 supplements. 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"; and "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.

AHPA 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 request for comments. Dietary ingredient safety has been adequately addressed numerous times in both this response and in DSHEA. As for non-dietary ingredients, FDA has authority to monitor the safety of actual food additives, through its existing regulatory authority.

In conclusion , AHPA 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 requests comments on how to best ensure that software and equipment used to direct and monitor the manufacturing process are properly designed, tested, validated and monitored.

It should be assumed that computer controlled manufacturing, upon installation, should be evaluated against manual operations. Validation controls, as mandated in CGMP regulations for drugs, should not be extended to regulations for dietary supplements.

8. Relevance of HACCP

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

Dietary supplement products are generally not subject to the type of hazards which HACCP is designed to control, such as food-borne illness. AHPA staff has met with FDA officials to clarify how HACCP might apply to dietary supplement products. While AHPA recognizes that FDA wishes to implement HACCP to an increasing degree in the conventional food industry, we also note that as a practical matter the only mandatory application of HACCP at the present is in the seafood industry.

HACCP is intended to identify and control hazards that are reasonably expected to occur, due to the nature of a product and the nature of the operations applied to it. These hazards most commonly are related to microbiological contamination, and are appropriate to products such as seafoods, meats, and poultry that provide a highly favorable environment for microbial growth and that are very likely to be subjected to microbial contamination during their shipment and processing. These are not the hazards most likely to be of concern with regard to dietary supplement products, and therefore HACCP is not viewed as the best means of assuring product safety for dietary supplements, as further discussed below.

Historically, dietary supplements have a remarkable history of safe use. In recent years, however, there have been a series of adverse events related to ephedra-containing products marketed for weight loss or sports nutrition. These events appear to be related in some cases to excessive use of the product and in other cases to individual susceptibility to the known physiological effects of ephedra, caffeine, and related ingredients which are commonly used together in such products. The industry has proposed warning labels which are almost universally used, and has proposed dosage limitations which are less uniformly observed. This is not a type of safety issue which is addressed either by CGMPs or HACCP, but requires broader policy-making.

9. Appropriateness of Broad CGMP Regulations

The agency requests comments on whether broad CGMP regulations will be adequate, or whether it will be necessary to address the operations of particular segments of the dietary supplements industry.

The differences between distinct segments of the dietary supplement industry, such as manufacturers or distributors of raw materials or finished products, are no more pronounced than similar entities in the food industry. AHPA believes that the Industry Draft provides adequate guidelines to each such segment sufficient to effectively ensure that dietary supplements are what they are represented to be and are safe for their intended use.

Respectfully submitted,

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