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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, MD 20857

RE: Docket 96N-0417
Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements

These comments on FDA's Advance Notice of Proposed Rulemaking (ANPR) regarding Good Manufacturing Practices (GMPs) for dietary supplements are submitted by the Council for Responsible Nutrition (CRN), a trade association representing the dietary supplement industry.

CRN's membership includes 84 companies engaged in the manufacture, distribution, and marketing of dietary supplements. Our membership covers the full range of companies from bulk ingredient manufacturers through finished product manufacturers, packagers, and marketers, and includes companies manufacturing all types of products included in the definition of dietary supplements. CRN member companies include many manufacturers of national brands of dietary supplements, and also includes the large private-label manufacturers who produce the vast majority of the store-brand dietary supplements available in supermarkets, drugstores, discount department stores, and health food stores. Attached is a list of CRN's current member companies.

96N-0417

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DSHEA authorizes FDA to establish GMPs for dietary supplements

The Dietary Supplement Health and Education of Act of 1994 (DSHEA) contains several provisions relating to GMPs. According to DSHEA, a dietary supplement is adulterated under Section 402 of the FD&C Act if it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations. Further, FDA is specifically authorized to prescribe good manufacturing practices for dietary supplements. DSHEA requires that such regulations be modeled after current good manufacturing practice regulations for food. DSHEA provides that, if GMP's are established, they must be established through formal notice-and-comment rulemaking.

Industry response to DSHEA: Submitted draft GMPs to FDA

The Council for Responsible Nutrition (CRN) developed GMP guidelines for its members in 1986 based largely on drug GMP's, but with some modifications. That CRN document was provided to the U.S. Pharmacopoeia (USP) when USP was developing standards for vitamin and mineral supplements, and formed the basis for the USP manufacturing guidelines for supplements.

Following the passage of DSHEA, which authorized FDA to establish dietary supplement GMPs "modeled after" food GMPs, CRN's Industry Quality Standards Working Group met several times in 1995 to work on a new set of GMPs meeting the specifications of DSHEA. Other associations were also invited to participate, and representatives of those associations did participate actively in the process of developing draft GMP regulations which could be supported by the industry. Cooperating associations included the National Nutritional Foods Association, the American Herbal Products Association, and the Utah Natural Products Alliance.

CRN's Industry Quality Standards Working Group started by closely examining the food GMP's (21 CFR 101.10) and considering whether these were sufficient or whether additional features were required to constitute useful and credible GMP's for dietary supplements. In November 1995, CRN and the other associations jointly submitted a set of draft GMP's to FDA for consideration.

In July of 1996, FDA notified the industry that the agency found the industry draft to be credible and useful, and that the agency intended to publish is as an Advance Notice of Proposed Rulemaking (ANPR). In February of this year, FDA published the industry draft GMP document as an ANPR, with comments due by May 7. The comment date was extended to June 6 after several industry groups including CRN requested an extension. The extension requested was 90 days, but only a 30-day extension was granted.

CRN is responding in a timely fashion to the ANPR with these comments, but wishes to emphasize the need to provide for additional systematic review and consideration of all aspects of the ANPR. This is further discussed in the **Conclusions** section of these comments. The industry draft GMPs alone pose a number of highly technical and complex issues which may not yet have been fully explored by all segments of the industry. In addition, the nine questions FDA has raised in the ANPR are significant ones which raise substantial issues regarding the appropriate scope of the food model of GMPs. CRN is concerned that some of FDA's questions suggest that the agency has an inappropriately broad view of the scope of issues which can appropriately be covered by food GMPs. The industry cannot and will not support GMPs that go beyond what is authorized by DSHEA. Several issues raised by FDA appear related to the agency's experience with drug models rather than food models of GMPs.

Comments on provisions of draft GMPs

CRN members have continued to discuss and evaluate the draft GMPs, with attention to detail, and on their behalf CRN wishes to suggest some specific amendments to the draft provisions, as outlined below.

Definition of "batch" or "lot": The definition of "batch or lot" in item (b) is not appropriate for continuous processes and needs to be amended to permit for such processes. The word "and" should be changed to "and/or" following "within specified limits", so that a batch or lot is defined as "a specific quantity of a finished product or other material that is intended to have uniform character and quality, within specified limits, and/or is produced according to a single manufacturing order during the same cycle of manufacture."

Definition of "rework": In item (s) of the definition section, the term "clean" when used in the context of "rework" is undefined and should be omitted. The requirement that the material be "unadulterated" is sufficient and covers the concept of cleanliness.

Personnel: In Section (b), change "include" to "may include." This will make it clear that items 1-9, listed in (b), are given as examples of methods for maintaining cleanliness, but are neither binding nor all-inclusive.

Plant and Grounds: In Section (a), change "include" to "may include." This will make it clear that items 1-4, listed in (a), are given as examples of methods to achieve adequate maintenance of grounds, but are neither binding nor all-inclusive.

Sanitation of Buildings and Facilities: The requirement in (b)(1) that cleaning compounds and sanitizing agents "shall be free from undesirable microorganisms and shall be safe and adequate under the conditions of use" is appropriate, but the following sentence describing the means of compliance is unnecessary. The manufacturer should determine the appropriate means of assuring compliance.

In Section (b)(3), change "including" to "which may include." This will make it clear that items (i) through (iv) are given as examples of methods to protect ingredients in outdoor fermentation vessels, but are neither binding nor all-inclusive.

In Section (d), the term "potable water" should be replaced with "potable or a higher quality quality water."

In Section (g), retain the current wording, "may be accomplished by." This makes it clear that items 1-4 are given as examples of features of adequate toilet facilities, but are neither binding nor all-inclusive.

In Section (h), retain the current wording "may be accomplished by providing." This makes it clear that items 1-6 are examples of features of adequate hand-washing facilities, but are neither binding nor all-inclusive.

Equipment and Utensils: Item (a)(5) should refer to "equipment that <u>is used in</u> the manufacturing or product handling area...." This paragraph currently refers incorrectly to "equipment that is <u>in</u>" the area.

In item (b)(11), the requirement for a "log" to document major equipment cleaning and use is too specific and therefore inappropriate, since cleaning can be appropriately documented without reliance on a log.

Quality Control and Laboratory Operations: In the section on product dating, in (c) and (c)(1), some CRN members prefer to refer to "shelf life dating" rather than "expiration dating." Although DSHEA refers directly

to "expiration date labeling," CRN recommends using a combined phrase such as "expiration date labeling or shelf life dating" in the section heading and in (c)(1).

Production and Process Controls: Under (a)(2)(vi) and (b)(2)(vii), there is mention of theoretical yields. These two sections should include the phrase "if possible", since calculating a theoretical yield on a lot by lot basis is not possible for continuous operations.

Under (a)(2)(vii), there is a requirement that the master production and control records shall include, as appropriate, a description of the product container(s), closure(s), and other packaging materials, including positive identification of all labeling used. In order to clarify that this requirement applies only to labeling used in finished packaging, this language needs to be clarified by changing the phrase "of all labeling used" to "of all labeling used in finished packaging."

In Section (c)(7)(iv), regarding the test of identity, it should be clear that the examples given of possible tests are only examples, and that it is up to the manufacture to select the appropriate test. This could be accomplished by putting a period after "identity" in line 6 of this section, and starting a new sentence with "Examples of appropriate tests may include chemical and laboratory tests....(etc)."

Under (d)(13) the phrase "as necessary" should be added to the end of the last sentence or the phrase "in batch processing" should be added to the beginning of the last sentence, to take continuous manufacturing operations into account.

Under (d)(16)(ii), the phrase "or caustic" should be added after "controlling the amount of acid" to allow for the other alternative in controlling pH.

CRN Response to FDA Questions

In publishing the ANPR, FDA posed a number of additional questions. CRN believes many of these questions address issues which go beyond the scope of food GMPs. CRN wishes to note that the requirement of DSHEA that dietary supplement GMPs be "modeled after" food GMP regulations is quite specific and must be honored. The industry will strongly oppose any effort to circumvent the intent of DSHEA by imposing requirements similar to those required for drugs. FDA's questions appear to be tending in this direction, or in some cases even going beyond what is required under drug GMPs.

1. **FDA QUESTION:** Is there a need to develop defect action levels (DALs)? FDA offers the opinion that the existing DALs for spices would probably be inappropriate for application to botanicals used as dietary supplements because the quantity of a botanical used as a supplement is likely to be greater than the quantity used as spices and flavorings.

CRN RESPONSE: DALs may need to be developed for some non-synthetic ingredients of dietary supplements, particularly botanical products which are subject to the same types of defects as are other natural products, such as spices. DALs are by definition unavoidable contaminants, and acceptable tolerance levels can be established only through a careful process of analyzing and quantifying the levels that occur in various products. Some industry members who worked with the CRN Industry Quality Standards Working Group in preparing the draft GMPs also have worked with the spice trade in establishing DALs for spices and are fully aware of the procedures normally utilized.

The draft GMP's already contain an extensive section on DALs, indicating that products need to conform to any DALs that are established. The actual establishment of levels, however, should not be undertaken as

part of the process of developing GMPs, but should be addressed in separate procedures, as were DALs for other food product categories.

2. **FDA QUESTION:** What testing requirements would be needed to provide positive identification of dietary ingredients, particularly plant materials?

CRN RESPONSE: The identity testing required will depend on the physical form of the ingredient, in the case of plant materials. The GMP document requires at least one test of identity, but selection of the test should be left to the judgment of the manufacturer. Some options are set forth, including chemical and laboratory tests, gross organoleptic analysis, microscopic identification, or analysis of constituent markers.

3. **FDA QUESTION:** Is a certification from a supplier sufficient to assure that a dietary ingredient is not contaminated with filth, contaminants, pesticide residues, or other impurities?

CRN RESPONSE: Yes, a certification is sufficient, provided the reliability of the supplier has been confirmed, as required by the GMP document. This provision is in keeping with the food GMP regulations, which allow a manufacturer to rely on certification of a supplier that products do not contain microorganisms or filth or other foreign material, as an alternative to direct testing of the raw materials or the final product.

4. **FDA QUESTION:** Are standard operating procedures needed to assure that procedures are followed on a continuing basis?

CRN RESPONSE: The GMPs as drafted require written procedures to be established in many instances. At the option of the manufacturer, these written procedures may take the form of SOPs, but there is no need to specifically require SOPs.

5. **FDA QUESTION:** Should there be a requirement that reports of injuries or illnesses received by a firm should be evaluated by competent medical authorities to determine whether follow-up action is necessary to protect the public health?

CRN RESPONSE: Dietary supplements are defined as foods. Consumer reports of adverse reactions are highly variable and generally relate to minor complaints. The GMPs as published already address the handling of complaint files in a manner which should be adequate for foods, including dietary supplements. A requirement that reports of illnesses or injuries be evaluated by a competent medical authority would not only go beyond food GMPs but would in fact go beyond the procedures required in drug GMPs. Such a requirement would be inappropriate for application to dietary supplements.

6. **FDA QUESTION:** Should there be a requirement for establishing procedures for responding to potential safety concerns?

CRN RESPONSE: This is an issue that may require additional discussion, in the context of ongoing FDA/industry efforts to respond effectively to safety issues which may arise. However, we believe this issue goes beyond the scope of GMPs and is not appropriate for treatment in this document.

7. **FDA QUESTION:** What controls are needed for computer assisted operations?

CRN RESPONSE: Reasonable manufacturer controls are required to evaluate whether computer controls are operating as planned. This should not extend to "validation" of operations as may be required under drug GMPs. If necessary, a new paragraph (a)(10) could be added under **Equipment and Utensils**, as follows:

"When computers are used as part of an automated production system having a significant and direct impact on product safety, the ability of the computer software programs to perform their intended function(s) shall be confirmed by adequate and documented testing."

8. **FDA QUESTION:** Would HACCP (Hazard Analysis Critical Control Points) be a better approach than GMP's?

CRN RESPONSE: HACCP is not a substitute for GMPs, but a system of safety assurance which is ideally superimposed on an operation already based on strong GMPs. Therefore CRN and its members do not view HACCP as an alternative to GMPs.

CRN and its members have sought out extensive information about HACCP, and staff has met with FDA HACCP officials to attempt to better understand how HACCP might apply to dietary supplement products. While CRN 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 applications of HACCP at the present time apply to seafoods, meats, and poultry. The vast majority of the food industry is not covered by a HACCP plan.

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. The hazards most commonly considered in HACCP plans are related to microbiological contamination, and are appropriate to products such as seafoods, meats, and poultry that are susceptible to contamination and that provide a highly favorable environment for the growth of microbes which may be present.

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.

Historically, dietary supplements have a remarkable history of safe use. Some adverse events have been due to manufacturing errors, and would have been best prevented by good GMPs of the type drafted by the industry and published by FDA in this ANPR. One incident, for example, related to a selenium product which mistakenly contained many times as much selenium as indicated on the label. This kind of manufacturing error can be addressed by careful attention to quantification of ingredients, including calculation of expected yield and actual yield from that ingredient, as set forth in the draft GMPs.

Another more serious and more widespread outbreak of adverse reactions was due to a contaminant produced in a single foreign manufacturer's process of making tryptophan. The tryptophan associated with the outbreak apparently met both Food Chemicals Codex and USP standards, and was in fact marketed in some European countries as a prescription product. Whether GMPs or other procedures could have avoided that event has been widely discussed in the years since the outbreak, with no resolution that CRN is aware of. This is not an issue unique to tryptophan or to dietary supplements, but has potential application for any food or drug ingredient. In any case, HACCP would not have been more likely than good GMPs to prevent a unique event of this type.

In recent years, there have been a series of adverse events related to ephedra-containing products. 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 have been used together in such products. The industry has implemented warning labels and dosage limitations. FDA has been considering regulatory action in this area for several years, has convened two special advisory groups (one in 1995 and one in 1996), and has just this week published proposed regulations relating to the safety of

ephedra-containing products. This is not a type of safety issue which is addressed either by GMPs or by HACCP, but requires broader policy-making.

CRN and its member companies are convinced that the problems that may potentially occur in this industry are not the kinds of problems HACCP is primarily designed to address. We believe appropriate GMPs are the best means of assuring the safety, quality, and composition of dietary supplements and of dietary supplement ingredients.

9. **FDA QUESTION:** Is one set of GMP's appropriate for a broad spectrum of firms, from raw material suppliers to manufacturers of finished products to packagers?

CRN RESPONSE: The Statement of Purpose included in the industry draft GMPs specifically recognizes that the category of dietary supplements as defined by DSHEA includes "a broad spectrum of product forms and a broad spectrum of dietary ingredients." Many product forms are also included, such as tablets, capsules, softgels, gelcaps, liquids, and other forms including--under some conditions--conventional food forms. The single set of GMPs drafted by the industry is intended to encompass all of these types of products.

A number of suppliers as well as finished product manufacturers, representatives of smaller companies as well as larger companies, and manufacturers of botanical dietary supplements as well as vitamin products were involved in the development of these GMPs. Representatives of the full spectrum of companies appear to believe that these GMPs are appropriate for the entire industry. However, if individual companies or groups of companies were to bring issues to light that need to be separately addressed, the GMPs could easily accommodate subsections dealing with unique issues.

Conclusions: Need for Workshops and Further Evaluation

CRN member companies, and the member companies of several other associations, have been closely focussed on GMP issues for more than two years, as they initially prepared and sought industry agreement on the draft document and as they have repeatedly subjected it to detailed analysis. Even after that amount of attention, every meeting or conference call reveals new questions which require extensive discussion and evaluation. It must be appreciated that a mandatory GMP affects every aspect of company operation, and that even seemingly small points can be critical to the company's ability to confidently comply with the requirements while maintaining an efficient operation. The continuing emergence of important questions strongly suggests to CRN that there is a need for additional discussion before this process goes to the next step of a proposed rule.

While CRN and the other associations have sought to fully involve their member companies in this process, it must also be recognized that there are many companies in the industry which do not belong to any of our associations. Some of those companies have only recently learned of the GMP document, through the ANPR, and have already submitted critical comments to the agency. GMPs are so important to the day-to-day operations of all dietary supplement companies that it is crucial for all companies to have an opportunity to thoroughly examine and evaluate the proposal, in light of their own product characteristics.

For these reasons, CRN strongly urges FDA to enter into a cooperative effort with the industry trade associations to co-sponsor a number of workshops which will permit thorough discussion and evaluation of each of the provisions of the GMP document, and that these workshops be considered as input to the content of a proposed rule. It is our experience that at least a full day of intensely concentrated discussion is needed in order to cover just the most critical provisions, and two days may be required if all the points of concern raised in this document are to be covered in a meaningful way.

These guidelines regarding timing would apply only if the purpose of the meetings is to review the industry draft GMPs. Discussion of the additional points raised by FDA would require additional time, in our opinion.

Following the workshops described above and incorporation of amendments that might emerge from those meetings, we believe FDA could proceed to a proposed regulation based on the industry draft with confidence that it would be feasible for all segments of the industry and appropriate to assure that products have the purity, quality, and composition they are represented to have.

The industry is united in its concern about the direction of many of the points FDA raises in its additional questions, either because the questions are not appropriate for resolution in the context of GMPs or because the GMP approach suggested by the FDA question is more drug-based than food-based. CRN firmly believes it would be inappropriate for FDA to proceed to a proposed rule with any GMP document that goes substantially beyond the industry draft. If FDA develops an approach significantly different from or expanded beyond the industry draft, CRN believes any such alternative approach should logically be the subject of another ANPR.

CRN and the other industry associations have made every effort to be helpful in facilitating the process of developing dietary supplement GMPs. We have acted in good faith, and our member companies have given serious consideration to the scope of GMPs necessary for our products. We hope that FDA will give due consideration to the time and effort that has gone into this process, and to the expertise that our member companies bring to bear on these issues. Accordingly, we urge FDA to make a commitment to jointly sponsored workshops to seek further clarification of appropriate GMP provisions, to incorporate amendments that are likely to emerge from those meetings, and then to propose regulations closely based on the industry draft as modified by further discussion.

Dietary supplement GMPs will affect the operations of every company in every segment of the industry, and a joint FDA/industry effort to help educate manufacturers as well as solicit more information from them could be extremely valuable in assuring that all issues are fully considered.

Sincerely,

V. Annette Dickinson, Ph.D.
Director of Scientific and Regulatory Affairs

CRN MEMBERSHIP LIST

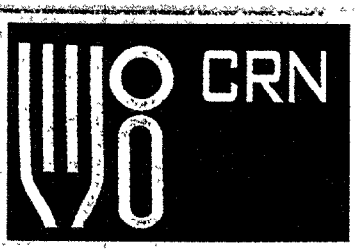
Voting Members	Location
Accucaps Industries Limited	Canada
ADM Bioproducts	Decatur, IL
American Home Products Corporation	Madison, NJ
American Laboratories, Inc.	Omaha, NE
Anabolic Laboratories, Inc.	Irvine, CA
APIC USA, Inc.	Westmont, IL
B&D Nutritional Ingredients, Inc.	Carlsbad, CA
BASF Corporation	Mount Olive, NJ
Banner Pharmacaps	Union, NJ/ Chatsworth, CA
BASF Corporation	Mount Olive, NJ
Bayer Corporation	Morristown, NJ
Bio San Laboratories Inc.	Derry, NH
Biotron Laboratories, Inc.	Centerville, UT
Botalia Pharmaceutical, Inc.	Boulder, CO
Capsugel	Greenwood, SC
Chugai Boyeki (America) Corporation	New York, NY
Colorcon	West Point, PA
Crompton & Knowles Ingredient Technology Corporation	Mahwah, NJ
Daiichi Fine Chemicals, Inc.	Lincolnshire, IL
EM Industries, Inc.	Hawthorne, NY
E. T. Horn Company	La Mirada, CA
East Earth Herb Inc.	Eugene OR
Eastman Chemical Company	Kingsport, TN
Eisai U.S.A., Inc.	Teaneck, NJ
Essential Nutrient Research Co., Inc. (ENRECO)	Manitowoc, WI
FMC Corporation	Philadelphia, PA
Fortitech, Inc.	Schenectady, NY
Gail Becker Associates, Inc.	Great Neck, NY
Gallard-Schlesinger Industries, Inc.	Carle Place, NY
General Nutrition Products Inc.	Greenville, SC
Genzyme Corporation	Cambridge, MA
Golden Neo-Life Diamite International	Fremont, CA
Hall Laboratories, Inc.	Portland, OR
Health for Life Brands, Inc.	Syracuse, NY
HealthComm International, Inc.	Gig Harbor, WA
Henkel Corporation	LaGrange, IL
Inter-Cal Corporation	Prescott, AZ
Kemin Foods, L.C.	Des Moines, IA
Leiner Health Products Inc.	Carson, CA
Lonza Inc.	Fair Lawn, NJ
Mary Kay, Inc.	Dallas, TX
McNeil Consumer Products Company	Ft. Washington, PA
Mendell, Inc.	Patterson, NY
M.W. International, Inc.	Hillside, NJ

Nature's Bounty, Inc.	Bohemia, N
Nutraceutical Corporation	Ogden, UT
Nutrasweet Kelco Company	San Diego, CA
Nutrilite Products, Inc.	Buena Park, CA
Nutrition 21	San Diego, CA
Nutro Laboratories, Inc.	South Plainfield, NJ
OmegaTech, Inc.	Boulder, CO
Perrigo Company of South Carolina, Inc.	Greenville, SC
Pharmachem Laboratories, Inc. /H. Reisman Corporation	Orange, NJ
Phamanex	Simi Valley, CA
Pharmavite Corporation	Mission Hills, CA
Pure-Gar, Inc.	Tacoma, WA
Quest International	Hoffman Estates, IL
R.P. Scherer North America	St. Petersburg, FL
Rexall Sundown, Inc.	Boca Raton, FL
Rhone-Poulenc Inc.	Cranbury, NJ
Roche Vitamins and Fine Chemicals	Paramus, NJ
Seaborne, Inc.	Alpharetta, GA
Shaklee Corporation	San Francisco, CA
Specialty Minerals, Inc.	Easton, PA
Stauber Performance Ingredients, Inc.	Brea, CA
Takeda U.S.A., Inc.	Orangeburg, NY
Vitaline Corporation	Ashland, OR
Vitamin Healthcenters/ Optibal Nutrition	Marlton, NJ
VitaTech International, Inc.	Tustin, CA
Wakunaga of America Company, Ltd.	Mission Viejo, CA
Watson Foods Co., Inc.	West Haven, CT

Associate Members	**Location**
Adams, Harkness & Hill	Boston, MA
Chicago Center for Clinical Research	Chicago, IL
Herbert V. Shuster, Inc.	Quincy, MA
IP Container	Paterson, NJ
Loren D. Israelsen	Salt Lake City, UT
Natural Foods Merchandiser	Boulder, CO
SETCO, Inc.	Anaheim, CA

International Correspondent Members	**Location**
BASF AG	Germany
Japan Health Summit, Inc.	Japan
Kenko Sangyo Shinbun	Japan
Otsuka Pharmaceutical Co., Ltd.	Japan
Seven Seas Limited	England
Sue Akeroyd and Associates	Australia
Vitamex America, Inc.	Coronado, CA

70 Voting Members
7 Associate Members
7 International Correspondent Members



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