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NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

Better Health Through Responsible Self-Medication

June 6, 1997

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

RE: Docket No. 96N-0417 Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements

These comments are in response to a Advance Notice of Proposed Rulemaking (ANPR) for Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements published in the *Federal Register* [62(25):5700-5709] on February 6, 1997 and are submitted on behalf of the Nonprescription Drug Manufacturers Association Vitamin/Mineral Task Group. NDMA is a 116-year-old trade organization representing the manufacturers and distributors of nonprescription drugs, as well as, combination and single-ingredient vitamin and mineral products. Our members represent over 95% of the OTC marketplace by sales and, in the case of vitamin and mineral supplements, represent all of the major manufacturers and distributors of adult and children's products such as Centrum®, One-A-Day®, Theragran® and Unicap®, among others. NDMA members have had a longstanding interest in dietary supplements, their labeling, and health claims.

NDMA members, in general, support the proposal for Current Good Manufacturing Practices for Dietary Supplements as proposed by FDA in the ANPR. The document herein, provides FDA with comments on the CGMPs as written and with information on the issues raised for comment. The comments are organized in the outline on the following pages.

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Table of Contents

(. . . continued)

(. . . continued)

Executive Summary

1. NDMA members support the proposal for Current Good Manufacturing Practices (CGMPs) for Dietary Supplements as proposed by FDA with a few minor modifications.

2. Given the diversity of dietary supplement products and the differences in delivery systems from conventional foods, Current Good Manufacturing Practices for dietary supplements are necessary to assure that consumers are provided with quality, safe and unadulterated dietary supplement products.

3. CGMPs for dietary supplements should identify specific requirements of the manufacturing process without dictating how firms should comply with such requirements. Examples and/or clarification should be provided through the guidance document process.

4. Manufacturers are responsible for putting procedures in place to implement CGMPs and batch records are required to document the critical steps in the process. Further documentation should not be a required by regulation.

5. Regulations requiring review and reporting of adverse events, not mandated for foods, are not appropriate for dietary supplements in the abscence of demonstrated difference in their safety profile. Such initiatives would be counter to the spirit of DSHEA.

6. HACCP cannot take the place of GMPs. Food products using HACCP practice GMPs. Therefore, HACCP should not be considered to replace CGMPs for dietary supplements. The manufacturing process of dietary supplements does not have safety concerns outside of those controlled by the GMPs. For this reason, HACCP is not appropriately mandated for the dietary supplement industry.

7. FDA and industry should convene working meetings/discussions prior to publication of a proposed rule to clarify issues in the industry GMP proposal and also to discuss areas in FDA's request for information that FDA may wish to pursue after review of comments received.

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Detailed Comments

I. General Comments

In the February 6, 1997 advanced notice of proposed rulemaking for CGMPs for dietary supplements, FDA recognized the question as to whether there is a need for dietary supplement good manufacturing practices to be followed in the manufacturing and control operations for dietary supplements and dietary ingredients or whether part 110 (21 CFR part 110) is adequate for such products. As defined in the Food, Drug, and Cosmetic Act in section 201(ff), dietary supplements include a broad spectrum of product forms and a broad spectrum of dietary ingredients. Dietary ingredients may include vitamins; minerals; herbs or other botanicals; amino acids; other dietary substances used to supplement the diet; and concentrates, metabolites, constituents, extracts, or combinations of these. Product forms include tablets, capsules, softgels, gelcaps, liquids, and other forms including--under some conditions--conventional food forms. Given the diversity of these products and the differences in delivery systems from conventional foods, a separate set of good manufacturing practices are necessary to assure that consumers are provided with safe dietary supplement products: which are not adulterated or misbranded; which have the identity and provide the quantity of dietary ingredients declared in labeling; and which meet the quality specifications that the supplement is represented to meet.

The CGMPs proposed by industry and published in the ANPR are modeled after good manufacturing practices for foods. Provisions have been adopted, modified, or expanded as appropriate, considering the special requirements applicable to the manufacture of dietary supplements and dietary ingredients. Dietary supplements are classified as foods, and the Good Manufacturing Practices applicable to them are similar to those generally applicable to other foods.

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The CGMP regulations should identify specific requirements of the manufacturing process without dictating how firms should comply with such requirements. Acceptable approaches to complying with requirements in a regulation can be delineated by the agency in a guidance document. Table I shows a representative (not all inclusive) list of sections in the ANPR CGMP document which should clearly be identified as non-binding examples of how to comply with the stated requirements:

Table I:

Representative Examples of Sections to be Designated as Guidance Only

Section	Federal Register Page of ANPR	Subsection
Personnel	5701-5702	(b)(1) through (b)(9)
Plants and Grounds	5702	(a)(1) through (a)(4)
Plants and Grounds	5702	(b)(3)(I) through (b)(3)(iv)
Sanitation of Buildings and Facilities	5703	(g)(1) through (g)(4)
Sanitation of Buildings and Facilities	5703	(h)(1) through (h)(6)

One issue which is not mandated by the ANPR is expiration dating or shelf life. It is in the best interest of the consumer that a shelf life or an expiration date, whichever is appropriate for the dietary supplement, be required. Such a requirement will provide consumers with the knowledge and assurance that when products are purchased, they meet label claims.

II. Current Good Manufacturing Practices for Dietary Supplements

NDMA supports the industry draft Good Manufacturing Practices. Since its publication in the *Federal Register*, the document has been given close scrutiny and there are some areas which require clarification. These are detailed in this letter in the following format:

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Federal Register Page: referring to the February 6, 1997 ANPR.

As stated in Federal Register: Excerpts from the ANPR for comment and surrounding text to keep context together.

Suggested Revision: NDMA suggested changes with additions underlined and deletions ~~struck out.~~

Rationale: An explanation of the NDMA suggestions.

A. Definitions

1. Definition of Rework

Federal Register Page: page 5701, column two

As stated in Federal Register: (s) ``Rework'' means clean, unadulterated material that has been removed from processing for reasons other than insanitary conditions or that has been successfully reconditioned by reprocessing and that is suitable for use in the manufacture of a dietary product.

Suggested Revision: (s) ``Rework'' means ~~clean,~~ unadulterated material that has been removed from processing for reasons other than insanitary conditions or material that has been successfully reconditioned by reprocessing and that is suitable for use in the manufacture of a dietary product

Rationale: The addition increases the clarity of the definition.

B. Sanitation of Buildings and Facilities

1. Cleaning and Sanitizing Materials

Federal Register Page: 5702, column three

As stated in Federal Register: (1) Cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be free from undesirable microorganisms and shall be safe and adequate

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under the conditions of use. Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination.

Suggested Revision: (1) Cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be free from undesirable microorganisms and shall be safe and adequate under the conditions of use. ~~Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination.~~

Rationale: It should be the responsibility of the manufacturer to comply with the regulation. This description of how to comply with the regulation may be interpreted as too restrictive. Guidance, such as that deleted above, should be provided by the FDA through mechanisms other than regulation.

2. Water Supply

Federal Register Page: page 5703, column three

As stated in Federal Register: Potable water at a suitable temperature, and under pressure as needed, shall be provided in all areas where required for the processing of dietary products, for the cleaning of processing equipment, utensils, and packaging materials, or for employee sanitary facilities.

Suggested Revision: Potable water, as a minimum quality water standard, at a suitable temperature, and under pressure as needed, shall be provided in all areas where required for the processing of dietary

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products, for the cleaning of processing equipment, utensils, and packaging materials, or for employee sanitary facilities.

Rationale: This clarification permits the use of higher quality water to be CGMP. As it was written, higher quality water would not have been in compliance.

C. Equipment and Utensils

1. Design and Construction

Federal Register Page: page 5703, column two

As stated in Federal Register: (5) Equipment that is in the manufacturing or product handling area and that does not come into contact with a dietary product shall be so constructed that it can be kept in a clean condition.

Suggested Revision: (5) Equipment that is used in the manufacturing or product handling area and that does not come into contact with a dietary product shall be so constructed that it can be kept in a clean condition.

Rationale: A technical clarification to increase preciseness of the definition.

2. Sanitation of Equipment and Utensils

Federal Register Page: page 5704, column one

As stated in Federal Register: (11) A written record of major equipment cleaning and use shall be maintained in individual equipment logs that show the date, product and lot number of each batch processed. The persons performing the cleaning shall record in the log that the work was performed. Entries in the log should be in chronological order.

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Suggested Revision: (11) A written record of major equipment cleaning and use shall be maintained. ~~in individual equipment logs that show the date, product and lot number of each batch processed.~~ The persons performing the cleaning shall record ~~in the log~~ that the work was performed. ~~Entries in the log should be in chronological order.~~

Rationale: Use of a log is too restrictive and dictates how a manufacturer should implement a regulation. Such advice, if necessary, should be provided through other mechanisms such as guidance documents. The definition, as revised, allows room for innovative development to support record keeping requirements, and permits a manufacturer the flexibility to use batch records, computers or logbooks to maintain records without restrictions.

D. Quality Control and Laboratory Procedures

1. Expiration Dating

Federal Register Page: page 5704 column two

As stated in Federal Register: (1) Whenever a dietary ingredient or dietary supplement bears an expiration date, such date shall be supported by data and rationale to reasonably assure that the product meets established specifications at the expiration date.

Suggested Revision: (1) ~~Whenever~~ A shelf life or an expiration date for a dietary product, whichever is appropriate, shall be supported by data and rationale to reasonably assure that the product meets established specifications at the ~~expiration~~ specified date.

Rationale: It is in the best interest of the consumer that a shelf life or an expiration date, whichever is appropriate for the dietary product, be required. Such a requirement will provide consumers with the

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knowledge and assurance that when products are purchased, they meet label claims. Such dating is current practice within the vitamin/mineral industry.

E. Production and Process Controls

1. Master Production and Control Records shall include . . . (iv) Calculated Excesses

Federal Register Page: page 5704, column three

As stated in Federal Register: (iv) A statement concerning any calculated excess of dietary ingredient contained in a dietary supplement.

Suggested Revision: A statement concerning any calculated excess of dietary ingredient in a finished product intended for consumption by a consumer.

Rationale: This is not appropriate for dietary ingredients in a continuous manufacturing operation.

2. Master Production and Control Records shall include . . . (vii) Calculated Excesses Labeling

Federal Register Page: page 5704, column three

As stated in Federal Register: (vii) A description of the product container(s), closure(s), and other packaging materials, including positive identification of all labeling used.

Suggested Revision: (vii) A description of the product container(s), closure(s), and other packaging materials, including positive identification of ~~all~~ finished product packaging labeling used.

Rationale: This addition adds clarity and removes in process labeling which seems inappropriate from this definition.

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3. Batch Production on Control Records

Federal Register Page: page 5704, column three

As stated in Federal Register: (2)(vii) A statement of actual yield at the conclusion of manufacture and a statement of the percentage of theoretical yield, as appropriate.

Suggested Revision: (2)(vii) A statement of actual yield at the conclusion of manufacture and a statement of the percentage of theoretical yield, as appropriate or possible.

Rationale: This addition is needed because such calculations are not possible on a lot by lot basis for continuous manufacturing operations.

4. Manufacturing Operations

Federal Register Page: page 5706, column one

As stated in Federal Register: (13) Mechanical manufacturing steps such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting shall be performed so as to protect dietary ingredients and dietary supplements against adulteration. Compliance with this requirement may be accomplished by providing adequate physical protection of dietary products from contact with adulterants. Protection may be provided by adequate cleaning and sanitizing of all processing equipment between each manufacturing step.

Suggested Revision: (13) Mechanical manufacturing steps such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting shall be performed so as to protect dietary ingredients and dietary supplements against adulteration. Compliance with this requirement may be accomplished by providing adequate physical protection of dietary products from contact with adulterants.

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Protection may be provided by adequate cleaning and sanitizing of all processing equipment between each manufacturing step, as necessary.

Rationale: This addition allows for the inclusion of continuous manufacturing operations.

5. Manufacturing Operations

Federal Register Page: page 5706, column one

As stated in Federal Register: (16) Dietary ingredients and dietary supplements that rely principally on the control of pH for preventing the growth of undesirable microorganisms shall be monitored and maintained at an appropriate pH. Compliance with this requirement may be accomplished by any effective means, including employment of one or more of the following practices: (ii) Controlling the amount of acid added to the product.

Suggested Revision: (16) Dietary ingredients and dietary supplements that rely principally on the control of pH for preventing the growth of undesirable microorganisms shall be monitored and maintained at an appropriate pH. Compliance with this requirement may be accomplished by any effective means. ~~including employment of one or more of the following practices: (ii) Controlling the amount of acid added to the product.~~

Rationale: This modification allows for alternative methods to controlling pH.

F. Warehousing, Distribution and Post-Distribution Procedures

1. Storage and Distribution

Federal Register Page: page 5706, column two

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As stated in Federal Register: (2) Adequate distribution records shall be maintained and retained by the manufacturer at least 1 year beyond expected product shelf life, whereby an effective product recall can be achieved should one become necessary.

Suggested Revision: (2) Adequate distribution records ~~shall~~ will be maintained and retained by the manufacturer at least 1 year beyond the product's shelf life or expiration date, whereby an effective product recall can be achieved should one become necessary.

Rationale: The addition as reflect the mandatory nature of expiration dates as well as the need for a shelf life for dietary ingredients.

2. Reserve Samples

Federal Register Page: page 5706, columns two and three

As stated in Federal Register: An appropriately identified reserve sample that is representative of each batch of a dietary product should be retained and stored under conditions consistent with the product labeling until at least 1 year after the expiration date, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture.

Suggested Revision: An appropriately identified reserve sample that is representative of each batch of a dietary product should be retained and stored under conditions consistent with the product labeling until at least 1 year after the product's shelf life or expiration date, ~~or if no expiration date is identified on the product, for at least 3 years after the date of manufacture.~~

Rationale: Expiration dating or shelf life should be mandatory.

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3. Records Retention

a. Batch Records

Federal Register Page: page 5706, column three

As stated in Federal Register: Any laboratory, production, control or distribution record specifically associated with a batch of product shall be retained for at least 1 year after the expiration date of the batch, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture.

Suggested Revision: Any laboratory, production, control or distribution record specifically associated with a batch of product shall be retained for at least 1 year after the product's shelf life or expiration date. ~~or the end of the shelf life of the batch.~~

Rationale: Expiration dating or shelf life should be mandatory.

b. Raw Materials Records

Federal Register Page: page 5706, column three

As stated in Federal Register: (2) Raw material records shall be maintained for at least 1 year after the expiration date of the last batch of product incorporating the raw material, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture of the finished product.

Suggested Revision: (2) Raw material records shall be maintained for at least 1 year after the product's shelf life or expiration date of the last batch of product incorporating the raw material.~~, or if no expiration date is identified on the~~

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~~product, for at least 3 years after the date of manufacture of the finished product.~~

Rationale: Expiration dating or shelf life should be mandatory.

III. Issues Raised For Comment By FDA

In the February 6, 1997 Advance Notice of Proposed Rulemaking, FDA requests comments on specific issues related to the regulation of dietary supplements. NDMA is supplying comments related to vitamin/mineral products under the subheadings below, each representing an issue raised by the questions. While NDMA is supplying comments, it is our position that it is inappropriate to incorporate the concepts of these questions into CGMPs for dietary supplements. Dietary supplement products have demonstrated a consistent safety profile. The inclusion of the concepts in the nine issues raised by FDA, as regulation, particularly in the case of vitamin/mineral products, would not increase the safety of the products or the benefits of the products to consumers.

If, after the review of the comments responding to the ANPR, FDA should wish to pursue the issues raised for comment, an open dialogue should be held to facilitate the resolution of a workable solution for both FDA and industry. The issues should be addressed in workshops which would allow for open discussion and exploration of the issues prior to any further proposed rule.

A. Defect Action Levels

FDA has tentatively concluded that it would not be appropriate to apply the current defect action levels (DALs) to dietary supplements, and the agency is requesting comments that would assist in developing DAL for dietary supplements.

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NDMA agrees that DALs for dietary supplements using non-synthetic ingredients would be appropriate; however, such an undertaking would require a major time and resource commitment given the large number of diverse ingredients and should be discussed outside of the GMP rulemaking.

B. Testing Requirements for Identification of Dietary Ingredients

FDA requested comments on the technical and scientific feasibility for the identification of different types of dietary ingredients and asked for information on what constitutes ``adequate testing'' to identify different types of ingredients.

FDA should not specify testing in a regulation. Manufacturers should be responsible for defining adequate testing based on the dietary ingredients in products. Because of the broad range of dietary ingredients and ever-changing scientific advancements, such testing needs to be individualized for each manufacturer and if, required by regulation, would need constant updating. If it is deemed appropriate, FDA could provide guidance to industry through the guidance document development process.

C. Certificate of Analysis from Suppliers

For food (Sec. 110.80), it is CGMP for a manufacturer to accept certification from a supplier, that products do not contain microorganisms or filth or other foreign material that would adulterate the product, in lieu of direct testing or evaluation of the raw materials or final product. The same should hold true for dietary supplement products. FDA is seeking comment on whether certification will provide assurance that dietary ingredients are not contaminated, or whether specific testing requirements are necessary and would effectively ensure the safety and wholesomeness of these products.

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Suppliers should be qualified by confirming the certificate of analysis results. This procedure should be established by the manufacturer. Raw materials should be examined for potential contaminants; however, it is the responsibility of the manufacturer, who understands the ingredients, to qualify the supplier to insure that product is of the highest quality. Additional testing requirements would be overly restrictive and cost prohibitive in the absence of any recognized problem.

D. Standard Operating Procedures

FDA requests comment on whether the CGMPs need to require manufacturers to establish procedures for documenting that the prescribed procedures for the manufacture of a dietary supplement are followed on a day-to-day basis.

Manufacturers are responsible for putting procedures in place to implement CGMPs, and batch records are required to document the critical steps in the process. It is a matter of good business practice to insure the quality of a product through periodic review of records and quality control audits. In the absence of a demonstrable safety problem, dietary supplements should not be subjected to additional requirements over and above foods. Such requirements would not increase the safety of the product and benefit to consumers and would increase the compliance burden of both industry and FDA.

E. Evaluation of Adverse Event Reports

FDA requested comments on whether CGMPs for dietary supplements should require manufacturers to establish procedures for determining whether a reported consumer injury constitutes a serious problem and what actions are to

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be taken when serious problems are identified. FDA also requests comments on whether manufacturers should be required to establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients. (Note: This section responds to FDA's questions five and six.)

As demonstrated by the American Association of Poison Control Center's (AAPCC) data base, the reports of serious adverse events for vitamin dietary supplements are rare and have a comparable severity profile to foods. Table II compares the reports for vitamin supplements vs. foods/food poisoning in 1995.

Table II:
1995+ Reports to the American Association of Poison Control Centers Tess Database for Foods/Food Poisoning and Vitamins

Category	Total # of Exposures	Adverse Reactions	Outcomes				
			None	Minor	Moderate	Major	Death
Foods	67,084	3,387	7,121	12,929	2,893	79	0
Vitamins	45,952	1,935	15,985	4,139	335	20	1*

\+ 1995 is the most recent, publicly available data published by the AAPCC.

* The death in the vitamin category was associated with accidental ingestion of iron containing prenatal vitamins. FDA has addressed this issue in other rulemakings and published a final rule in January 1997 on the packaging and labeling of iron containing dietary supplements.

The total number of reports for vitamin products is lower than food products. While this is not surprising, given the greater use of food as compared to dietary supplements, it does demonstrate the fact that vitamins do not present a greater health risk to the general population than foods. Hence, dietary supplements should be subject to the same regulatory requirements as foods for review of adverse event and safety databases.

In 1995, the severity profile of the outcomes associated with vitamin use further demonstrates the safety of these products. Less than 1% of the exposures reported to the AAPCC database for vitamin supplements resulted

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in more than a minor outcome (moderate, major, or death). [Note: The total number of reports represents a small fraction of product use.]

Childhood poisonings with iron-containing supplements are an excellent example of how industry currently reviews safety databases for marketed products and takes action when necessary. In 1993, after reviewing safety information, NDMA and other industry members initiated a voluntary program for labeling, packaging and formulation for iron-containing dietary supplements. This program also had a public education component. FDA has subsequently issued a final rule to address this issue; however, in the absence of FDA regulation, the industry reviewed and addressed a public health concern. This demonstrates that FDA regulations for evaluation of adverse event databases is not needed for dietary supplements because such activity already occurs as needed.

NDMA has surveyed several manufacturers of vitamin/mineral products for specific information related to adverse events reported to companies. While Table IV does not encompass all NDMA members, it is representative of the types of profiles by the industry.

Table IV
Spontaneous Adverse Events Reportedly Associated with Vitamin/Mineral Products

Year	# of Products (SKUs)	# of Units sold	# of Adverse Events Reported	Outcome of Adverse Event Reports Appendix 1				
				None	Minor	Mod-erate	Major	Death
1995	55	23,000,000	1670	1265	403	2	0	0
1996	53	24,600,000	1579	1261	318	0	0	0

Note: Accidental ingestion or over ingestion is recorded as an adverse event if more than one tablet is consumed.

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This data supports that presented above from the AAPCC database. Adverse events reportedly associated with vitamin/mineral products are small in number relative to the number of units sold. The events are not serious with the majority of reports resulting in no outcome. The reports are usually associated accidental ingestion or over ingestion.

Vitamin/mineral dietary supplement manufacturers have mechanisms to evaluate adverse events reported to their company. Given the long history of marketing, the lack of safety issues, and a low incidence of adverse event reports, adverse event reporting and review regulations, not mandated for foods, are not appropriate for dietary supplements and vitamin/mineral dietary supplements, in particular. Such regulations would be costly and counter to the spirit of DSHEA.

F. Computer Validation

FDA requests comments on whether specific controls are necessary for computer controlled or assisted operations. FDA also requests comment on how best to ensure that the software programs and equipment used to direct and monitor the manufacturing process are properly designed, tested, validated, and monitored.

Such a stipulation could be included in CGMPs, as "Software programs and equipment used to direct and monitor the manufacturing process should be properly designed, tested, <u>evaluated</u> ~~validated~~ and monitored." Specific recommendations, if deemed necessary by FDA, on methodology should be addressed in guidance documents rather than in regulation. The manufacturer should have to determine what is appropriate for their particular operation.

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G. Hazard And Critical Control Point Analysis

The agency asks for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be more effectively addressed by a regulation based on the principles of Hazard Analysis and Critical Control Points (HACCP), rather than the system outlined in the industry submission.

Since the publication of the ANPR for CGMPs, NDMA has been researching HACCP. As an association of drug manufacturers unfamiliar with the concept, we have met with outside consultants, as well as, Darryl Schwalm and John Kvenberg in FDA's HACCP office to educate ourselves on the concept. Through these meetings and discussions, no benefit of a HACCP vs. GMP program has emerged. HACCP does not appear appropriate for the dietary supplement industry.

As indicated by the staff in FDA's HACCP office, the basis of HACCP is GMPs. Manufacturers of food products using HACCP still practice GMPs. HACCP cannot take the place of GMPs. HACCP addresses safety concerns for a particular industry and is individualized on a company-by-company basis.

HACCP addresses safety issues not directly covered by CGMPs which may be specific to a company or product. The manufacturing process for dietary supplements does not have the safety concerns which are not covered under GMPs. For this reason HACCP is not appropriately mandated for the dietary supplement industry.

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Further to this point, HACCP is an approach based the definition of critical control points where safety of the product may be disrupted. This is done through the determination of potential microbiological, chemical, or physical hazards in the manufacturing and delivery process. Theoretically, in any manufacturing process, hazards may be introduced and could be considered a critical control point. This, however, is not how HACCP is implemented.

From our meeting with FDA on HACCP, critical control points and hazards are determined through research on products, examination of recalls, and adverse event databases. The research will reveal the hazards that need to be controlled in the manufacture of the product. For the vitamin industry, as well as the supplement industry as a whole, historical data and the number of adverse event reports not associated with product misuse or abuse yield very little information to help make determinations regarding critical points in the manufacturing process where safety of the product may be disrupted.

Table III demonstrates that in 1995 the majority of the reports associated with vitamin supplements to poison control centers involved unintentional exposure and most occurred in children under age six. These are most likely accidental ingestions that resulted in minor outcomes.

Table III
Exposures Reportedly Associated with Vitamin Dietary Supplements to the American Association of Poison Control Centers in 1995

Total # of Exposures	Exposures in children < 6	Unintentional Exposure	Intentional Exposure	Other	Adverse Reaction
45,952	36,553	41,892	2,018	28	1,935

It cannot be determined from the available data which of the 356 cases in Table II resulted in the more serious outcomes listed in Table III.

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Prevention of unintentional exposure and product abuse (the most common type of an adverse event report which usually results in minor to no outcome) can not be addressed in the manufacturing process and are therefore not appropriately regulated by HACCP. Industry has a track record for evaluating such problems when they do occur and taking action to address the problem (e.g. iron-containing supplements). This has been done outside of a HACCP analysis of the manufacturing process. This further demonstrates that the HACCP approach to the safety of the manufacturing process is not an appropriate route of regulation of the dietary supplements manufacturing process.

H. Applicability of CGMPs to the Dietary Supplement Industry

The dietary supplement industry reviewed and agreed to the industry draft submitted to the FDA. This should be taken as evidence that the approach is suitable and acceptable to the entire industry. Such requirements should be applied to all products consumed by United States consumers including those imported into the country. A specific mention is requested, in the CGMP proposed rule, of the mechanism which will be employed to insure that these standards will be applied to all dietary products imported in to the U.S.

IV. Conclusions

The vitamin/mineral dietary supplement industry supports the regulatory construct of CGMPs outlined in FDA's Advanced Notice of Proposed Rulemaking with a few minor revisions. Dietary supplements CGMPs are necessary due to the difference in delivery systems from conventional foods but should be drafted based on food GMPs, as stated in DSHEA. The industry-submitted document achieves this goal.

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The nine issues raised by FDA suggest that the agency is considering broadening the scope of the GMPs beyond the intention of DSHEA. While the agency raises some interesting, theoretical issues in the questions, addressing the issues in the context of CGMPs for dietary supplements will increase the cost of products with no additional safety benefit to consumers because the products already have a demonstrated safety profile.

NDMA believes that it is in the best interest of the industry and FDA to discuss significant changes in the ANPR prior to the publication of a proposed rule. NDMA requests the opportunity to develop with FDA and the dietary supplement industry the structure and content of such dialogues.

NDMA supports FDA's and DSHEA's intentions in this rulemaking. If NDMA can be of further assistance, please contact my office at 202-429-9260.

Sincerely,

Patrice Wright

Patrice B. Wright, Ph.D.
Director, Pharmacology and Toxicology

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Appendix I

Definition of Outcomes

as Defined by the American Association of Poison Control Centers

1. No Outcome: The patient developed no symptoms as a result of the exposure.

   Minor Effect: The patient exhibited some symptoms as a result of the exposure, but they were minimal or no treatment was provided. The symptoms resolved rapidly and usually involve skin or mucous membrane manifestations. The patient returned to pre-exposure state of well beings and has no residual disability.

   Moderate Effect: The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated to treat the patient. Symptoms were not life threatening and the patient has returned to a pre-exposure state of well being with no residual disability or disfigurement.

   Major Effect: The patient exhibited some symptoms as a result of exposure. The symptoms were life threatening or resulted in residual disability or disfigurement.