International Pharmaceutical Excipients Council
Of The Americas

June 4, 1997

Dockets Management Branch
(HFA-305)
U.S. Food & Drug Administration
12420 Parklawn Drive, Room 123
Rockville, MD 20857

RE: Docket No. 96N-0417; current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements; Advance Notice of Proposed Rulemaking

Dear Sirs:

The following comments are submitted on behalf of the membership of the International Pharmaceutical Excipients Council of the Americas ("IPEC-Americas")

IPEC-Americas is an industry association. Its members are companies which produce or use excipients for drugs, cosmetics, foods, and/or dietary supplements sold in the United States.

Over 180 national and multinational firms are members of IPEC-Americas and/or its affiliate organizations in Europe and Japan. Many of these firms outside the U.S. export excipients for use in U.S. dietary supplements or export dietary supplements directly for sale in the United States. As a result, Council members have substantial interest in matters discussed in the Advance Notice of Proposed Rulemaking.

As we use the term "excipients" in connection with their use in dietary supplements, the term encompasses any substance other than dietary ingredients. Excipients are employed in the delivery system of dietary supplements for a specific purpose or purposes. For example, an excipient may be utilized to aid in the processing of the delivery system during its manufacture; others may protect, support, or enhance stability, bioavailability, or product acceptability. Excipients also assist in product identification and may enhance the

overall safety and potency of the dietary ingredients and the product itself during storage and use.

Excipients used in pharmaceutical preparations are required to be adequately qualified by their manufacturer and the manufacturer of the finished drug dosage form as part of good manufacturing practice. IPEC-Americas believes that the agency should do no less in connection with dietary supplements and thus should require dietary supplement manufacturers to adequately qualify all ingredients, including excipients, contained in their products.

Adequate qualification considers identity, safety, funtionality, manufacturing process, product performance, and stability. IPEC-Americas, therefore, supports the development of current good manufacturing practice (cGMP) regulations for dietary supplements, dietary ingredients, and raw materials.

In response to the issues raised in the ANPR, IPEC-Americas submits the following comments:

1. Dietary ingredient Defect Action Levels (DALs) - As noted earlier, excipients are essential components of dietary supplements but are neither intended to supplement the diet nor are they "dietary ingredients" as defined in Section 3 of the Dietary Supplement Health and Education Act of 1994. However, if an excipient is intended to be used in a dietary supplement, it must be qualified by its manufacturer as non-toxic and reasonably able to perform its intended function; and subsequently, by the manufacturer of the supplement, that it is safe and that it performs its intended function in the supplement dosage form. Apart from that qualification, however, IPEC-Americas believes that specific DALs are not necessary nor applicable to excipients that either are GRAS, approved food additives or the subject of USP monographs.

2. Identification of dietary ingredients - As in existing drug GMPs (21 CFR Parts 210-211), future dietary supplement GMPs should not detail test methods for identification. The language in sub part Production and Process Controls, section (c) (7) (iv) of the ANPR, covers the requirement sufficiently and allows for the science and technology available. Therefore, no further enhancement of this section is recommended.

3. Certificate of analysis from a supplier - Section 211.84 (d) (2) and (3) of the drug GMPs allow the use of a certificate of analysis from a supplier "provided the manufacturer establishes the reliability of the supplier's test result." Sub part Production and Process Controls, sections (c) (7) (i) to (v) of the ANPR, provide the same requirement using the same language. As a result, no expansion of this section appears to be indicated or necessary.

4. Need to document that a manufacturer follows procedures - Sub part Production and Process Controls, sections (a) and (b) of the ANPR, sufficiently cover the requirements to assure that standard operating procedures are followed. Therefore, no amendment to this section is recommended.

5. Reporting of injuries related to dietary supplement use - IPEC-Americas takes no position on this question, as it concerns dietary supplements and dietary ingredients rather than excipients directly. However, we note that reporting of injuries is not part of FDA's existing cGMP regulations for drugs, 21 CFR Parts 210-211, nor is reporting contained in the food GMPs, 21 CFR Part 110.

6. Need for requirements to identify, evaluate, and respond to potential safety concerns with dietary ingredients - IPEC-Americas believes that it is incumbent on a manufacturer of a dietary supplement to adequately qualify all ingredients contained in his product for safety and functionality. Further, the manufacturer should be required to evaluate and respond to any future questions regarding safety, which are determined by the agency to represent a potential hazard to human health. Consequently, we support this concept as set forth in the ANPR.

7. Need for specific controls for computer controlled or assisted operations - IPEC-Americas agrees that written control procedures are necessary and that they should be properly designed, tested, and validated as part of good manufacturing practice.

8. HACCP or GMPs for dietary supplements - IPEC-Americas submits that cGMP regulations, with their greater emphasis on product purity and safety, are more applicable to and appropriate for dietary supplements than HACCP regulations.

9. Need for more than one set of dietary supplement cGMP regulations - IPEC-Americas believes that one set of broad regulations would be preferable to separate regulations applicable only to individual types of dietary ingredients. Having numerous GMPs could subject many raw materials/dietary ingredients to multiple GMPs, thus adding unnecessary complexity in the manufacturing operations of excipients. We also question whether promulgation of multiple regulations is either necessary or economically justified in this era of limited corporate and U.S. government regulatory resources.

Finally we also would like to suggest that a definition for "adulteration"--based on the statutory definition set forth in section 402 of the FD&C Act-- should be included in the "definitions" section of any forthcoming regulations.

We appreciate the opportunity to comment and hope that our comments and suggestions will be useful to the agency.

Sincerely.

David R. Schoneker
Vice Chair for Science
& Regulatory Policy

enclosure: Roster of the IPEC-Americas Dietary Supplement Working Group

International Pharmaceutical Excipients Council
of the Americas

Special Dietary Supplement Working Group

Chair:

Ofelia U. Barretto
Director, Quality Assurance
Nutrilite Division Amway Corporation

Members:

Paquita E. Barnum, Ph.D.
Senior Research Scientist
Hercules Incorporated

Barbara Bentson
Senior Scientist
The Procter & Gamble Company

Janine Carlan
Regulatory Affairs Associate
FMC Corporation

Elke M. Clarke, Ph.D.
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General Manager, North America
EM Industries

Sidney A. Goode, Pharm.D.
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Dow Chemical Company

Alan Morrow
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B.F. Goodrich Specialty Chemicals

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R.P. Scherer North America

Staff Executive:

Alan Mercill
Secretary-Treasurer
IPEC-Americas Member Services