Cargill
Health & Food Technologies

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

August 11, 2003

RE: DOCKET NO. 96N-0417; GOOD MANUFACTURING PRACTICES IN MANUFACTURING, PACKING, OR HOLDING DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS: PROPOSED RULE

Dear Sir or Madam:

Cargill Health & Food Technologies ("Cargill HFT") is a leading developer, processor and marketer of science-based, healthy ingredients for food and dietary supplements worldwide. Cargill HFT is a business unit of Cargill Incorporated, an international marketer, processor, and distributor of agricultural, food, financial, and industrial products and services. We maintain that a robust and enforced system for good manufacturing practices ("GMPs") provides the critical infrastructure that ensures the successful delivery of high quality products to our customers and subsequently, to consumers.

We support the Agency's efforts to establish GMPs and urge the Agency to conduct an expeditious review of the comments filed during this open comment period in order to issue a final rule that will provide regulatory definition for the industry. Cargill HFT provides the following comments for consideration by the Agency:

1. **Dietary ingredient manufacturers should be subject to the proposed good manufacturing practices for dietary supplements.**

Cargill HFT supplies dietary ingredients to both food and dietary supplement finished product manufacturers. We believe in adhering to one GMP standard of highest quality for all our products. GMPs for both ingredient and supplement manufacturers help ensure safe and quality products and when effectively enforced on a global basis, will result in an industry that meets consumer needs and expectations for safe products. Therefore, we support the proposed rule that requires both dietary ingredients and finished dietary supplements to comply with the dietary supplement GMPs.

96N-0417

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2. Cargill HFT supports provisions for expiration dating in the final GMP regulation.

The proposed GMP regulations for dietary supplements do not require shelf life testing or expiration dating for dietary supplements. Cargill believes expiration dating is essential to the ability to market dietary supplements and dietary ingredients in today's business environment. Consumers expect and demand expiration dating, major retail chains will not accept dietary supplements without expiration dating, and most manufacturers have stability programs in place to support the establishment of shelf life or expiration dating. Cargill HFT urges FDA to reconsider in the final rulemaking the necessity for requiring expiration dating for dietary supplements.

3. Cargill supports provisions in the final rule that allow supplier qualification programs as an acceptable alternative to exhaustive finished product testing when assuring the quality of components and dietary ingredients.

Cargill HFT maintains that manufacturers of dietary supplements should be able to rely on an appropriate supplier qualification program for key material vendors. Such programs are essential to permit the finished product manufacturer to assess the reliability of the vendor and accordingly, determine the amount of incoming material testing that may be required to provide the necessary level of confidence that the material will meet specifications.

Vendor qualification programs may include plant visits and inspections, GMP audits or process reviews, verification of laboratory test results against certificates of analysis, and 100% inspection and testing of incoming materials for a specified period while reliability is being assessed. By extending process control mechanisms to suppliers, the manufacturer can make appropriate use of the expertise of the vendor and eliminate the need for extensive and duplicative testing of received materials. In a properly defined supplier/manufacturer relationship, testing completed by a supplier that has been qualified by the finished product manufacturer should be considered as reliable as testing performed by any other qualified laboratory.

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4. Cargill HFT supports the requirement of written procedures.

Written procedures are essential to the development and maintenance of a well-controlled production process. Written procedures are necessary for the definition, operation and documentation of a process control system, without which uniformity of operations cannot be assured and adequate training and supervision cannot be undertaken. Cargill HFT supports requiring written procedures in the following areas: training; cleaning and maintaining equipment and utensils used in the manufacture of dietary products; processes including the receipt, identification, examination, handling, sampling, testing and approval or rejection of raw ingredients and packaging materials; appropriate tests and/or examinations to be conducted that may be necessary to assure the purity, composition and quality of the finished product, and to establish release specifications; method for reprocessing batches or operational start-up materials that do not conform to finished goods standards or specifications; and procedures to assure that correct labels, labeling, and packaging materials are issued and used.

5. Section 111.20 lists design and constructions requirements for physical plants that may not be appropriate for closed processes.

Section 111.20 (d) outlines requirements for design and construction of the physical plant that results in the prevention of contamination of components, dietary ingredients, dietary supplements, or contact surfaces. These requirements appear to be based on drug GMPs for aseptic processes and are inappropriate as an overall requirement for all aspects of dietary supplement and dietary ingredient manufacturing facilities. For example, section (d) (1) requires smooth walls and ceilings. This may be appropriate for a final product packaging room but this is not necessary for areas of the plant that contain a closed processing system. We recommend modifying the final regulation by adding "as appropriate" throughout these provisions to allow for continuous or closed processing systems and processing criticality.

6. Terminology and provisions pertinent to "components" need clarification in the final rule.

In Section 111.35 (d), the proposed rule requires that all substances other than a "dietary ingredient" must be authorized by regulation when the "intended use... results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient". This could be interpreted to mean that each substance that eventually becomes a component of a dietary supplement must be food grade.

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It is not feasible to require that the starting materials used by bulk ingredient manufacturers be GRAS or approved food additives when initially introduced into the manufacturing process. Many raw materials are not food grade substances or approved food ingredients until after processing. We suggest that this provision be modified to ensure that "raw, starting materials" are not subject to the definition of component. Additionally, we suggest the final rule clarify that suppliers of components and "raw materials" should not be subject to GMPs for dietary supplements, but should in fact, comply with food GMPs.

7. Reserve samples and their retention time need clarification in the final rule.

Section 111.37 (b) (12) requires that "reserve" samples be kept for a minimum of three years. The proposed rule is not specific if this refers to in-process samples, final product samples, or both. Reserve samples of in-process materials are not commonly retained, and the cost of this additional requirement is not included in the economic analysis. In-process materials are not in finished form and are not presumed to be stable in their in-process form. Also, there are issues of storage, safety, and stability that would have a direct impact on the ability and need to retain in-process samples. There should not be a requirement to retain in-process samples.

Additionally, the final rule should be flexible in the establishment of three years as the retention time for final dietary ingredient samples as noted in Section 111.50 (h), which requires that reserve batch samples be kept for three years beyond date of manufacture. All ingredients do not have the same shelf life. We suggest that reserve samples minimally be kept one year beyond expiration dating.

8. Quarantine and approvals of components by Quality Assurance personnel as required in 111. 40 (a) (3) may not be feasible in continuous operations.

Section 111.40(a)(3) of the proposed rule requires that all components, dietary ingredients and dietary supplements be quarantined until released by the quality control unit. It is not feasible to quarantine incoming material in a continuous extraction and purification operation, such as one that could be built adjacent to a soy crushing or vegetable oil refinery that receives a continuous side stream flow from that operation. In such operations, quarantine and QC approval occurs later in the process after the material has been isolated and concentrated in a stable matrix suitable for holding. We recommended allowing for this type of operation by inserting "as applicable" into this section.

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9. **Batch record requirements need to allow for modified record-keeping options for continuous operations and more flexibility with reprocessing.**

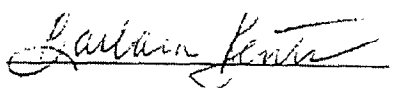
The requirements of Section 111.50 (c)(2)(5) and (6) are not easily adaptable to continuous processes, instead, appear to be intended for batch processes only. We request the agency consider how to allow for continuous processes when finalizing the requirements for batch record documentation. Continuous processes do not have defined steps that lend themselves to this type of batch documentation.

Section 111.50(c)(4) requires documentation of maintenance, cleaning, and sanitizing of equipment and processing lines used in producing the batch. Again, these requirements are uniquely suited for batch processes. For continuing processes, equipment maintenance, cleaning, and sanitizing records are typically retained in an equipment log. Cross-referencing the records of these activities should be an alternative to mandatory inclusion in the batch record.

Section 111.50(f) states "You must not reprocess a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals". Reprocessing should be allowed if there is a scientifically valid process to correct the defect that ensures the identity, purity, quality, strength and composition of the finished product.

We appreciate the opportunity to comment and look forward to the finalization of the rulemaking process for dietary supplement GMPs.

Sincerely,



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