Shaklee
Creating Healthier Lives™

Shaklee Corporation

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VIA FEDERAL EXPRESS

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

Re: Docket # 96N-0417, Current Good Manufacturing Practices in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements.

For nearly 50 years, Shaklee Corporation ("Shaklee") has been manufacturing and distributing innovative, high-quality dietary supplements. As long as it has made dietary supplements, Shaklee has manufactured its products in strict conformity with the highest quality standards. Shaklee's state-of-the-art manufacturing facility operates under near-pharmaceutical CGMPs. Every year, Shaklee conducts approximately 85,000 laboratory and quality assurance tests on raw ingredients and finished products. Shaklee's ingredient suppliers and contract manufacturers are held to equally high standards.

As a leader in quality manufacturing in the dietary supplement industry and a proponent of appropriate good manufacturing practices for dietary supplements, Shaklee supports FDA's initiative to implement standards in this area. While Shaklee believes the proposed Current Good Manufacturing Practices (cGMPs) are a good foundation for discussion, there are a number of areas in which they must be amended to ensure that they promote safe, consistent, and reliable manufacturing of dietary supplements, while not imposing unnecessary costs and burdens on industry.

The first section of these comments addresses two areas of particular concern to Shaklee: the proposed requirement to test every batch of finished product and the prohibition against relying on third-party GRAS notification petitions to support GRAS status of ingredients. The second section covers a number of other changes and/or clarifications that Shaklee believes are necessary to ensure that the cGMPs are effective and not overly burdensome.

I. Issues of Particular Concern

A. Product Testing – Proposed Section 111.35(g)

Section 111.35(g) mandates testing of each finished batch for identity, purity, quality, strength, and composition or, in the case of specifications for which there is no

scientifically valid analytical method, employing a combination of incoming ingredient testing and in-process testing to ensure compliance with specifications.

The proposed 100% testing requirements precludes reliance on other valid, well established methods for ensuring product quality, including vendor qualification and raw material certification, manufacturing process qualification followed by ongoing statistical process control, and selected in-process and finished product testing. The proposed mandatory testing requirements would increase the number of tests that Shaklee and other manufacturers of dietary supplements would have to conduct. The burden and cost of the additional testing that Shaklee would need to undertake are significant (see infra p. 4) and would not meaningfully advance the primary purpose of the regulations as identified by FDA – protecting consumers from adulterated and misbranded product.

Currently, Shaklee ensures the identity, purity, quality, strength, and composition of its incoming raw materials through a comprehensive program to qualify suppliers and certify raw materials. Elements of the program include, but are not limited to:

- Evaluating a potential supplier's responses to a detailed questionnaire that covers all aspects of its raw material manufacturing process and related cGMP issues

- Conducting an onsite cGMP compliance audit of the potential supplier's manufacturing facility (or harvesting, storage, sorting, cutting and milling sites for botanical items), including QC inspection/testing laboratories

- Performing a review of the potential supplier's specifications and actual test results (Certificates of Analysis) for the material

- Testing representative samples of three different production-size lots of the items by Shaklee scientists to assure they comply with all physical, chemical and microbiological specification parameters

- Using the material in trial batches of finished product to assure that it processes well and functions as intended

Upon meeting the qualification criteria, the supplier is considered qualified to supply the particular raw material. The first two lots of the raw material that are subsequently received at our plant are fully tested for compliance with every specification parameter, bringing the total number of lots tested to five. If there have been no testing failures, the material from this particular supplier is considered to be certified. This means that any future shipment may be released based on the receipt of a complete Certificate of Analysis (i.e. one that covers all parameters specified by Shaklee) if it successfully passes at least one appropriate identity test or assay and meets all specified microbiological requirements. The supplier's qualification/certification status is maintained indefinitely,

provided that at least one lot per year is tested for and successfully meets all specification parameters and audits of the supplier do not identify any significant cGMP compliance issues. Any raw material provided by a supplier which does not meet the qualification/certification criteria described above is subject to 100% testing.

In addition, Shaklee employs a statistically based process qualification and testing program to ensure that its dietary supplement products meet all applicable specifications. In addition to the use of certified raw materials from qualified suppliers, as described above, this program may include, but is not limited to:

- Using suitable, well maintained, clean and calibrated production equipment
- Preparing and using written master and production batch records and written SOPs which are followed and documented by properly trained employees
- Formulating and using vitamin and mineral premixes
- Conducting protocol-based process qualification studies involving one or more batches to determine optimum processing conditions (material addition sequence, mixing speeds, times, temperatures, etc.)
- Conducting mixology studies to assure batch uniformity, with particular concern for label claimed ingredients
- Calculating yield at appropriate steps in the manufacturing process
- Conducting comprehensive QC testing of the first 30 production lots followed by statistical analyses to assure that the process is operating under statistical control. (If the data shows that the process is not operating under statistical control, then further adjustments are made until this is achieved, based on 30 consecutive production lots.)
- Moving to reduced QC testing of selected parameters once statistical control is achieved

The frequency of testing varies from product to product based on production run size, but it may apply to two out of three lots (67%) up to six out of seven lots (86%). The testing frequency established remains in effect as long as there are no test failures or other indicators that the process is no longer operating under statistical control. If such failures or indicators occur, the product is returned to its original comprehensive QC testing schedule.

The proposed requirement to test every finished batch and, in the absence of scientifically valid analytical testing, to test incoming components, would substantially increase Shaklee's testing costs. Currently, Shaklee manufactures more than 2,000 batches of finished dietary supplement products in-house. Shaklee performs a variety of tests on finished product, including mineral assays, vitamin assays, chemical assays, mineral dissolution, disintegration, organoleptics, coliforms, e. coli, yeast and molds, TMA, and salmonella. The cost of the different tests ranges from approximately $7 to $ 30 per test. Currently, Shaklee's performs approximately 25,000 tests annually on finished product for a cost in excess of $ 375,000. Mandatory testing of every batch of finished product would increase Shaklee's costs by more than 60%, calculated solely on a cost-per-test basis. In addition, there will be one-time costs incurred in drafting and implementing the new testing procedures.

Shaklee recommends that FDA exempt manufacturers from the requirement to test each finished batch pursuant to section 111.35(g) if they have a qualified manufacturing process that meets the basic elements described below. To qualify for the exemption, the manufacturer must have written procedures for each stage of the process – including raw material certification, production, and finished product analysis – and a written plan for qualifying this process.

Raw material certification. A manufacturer must have a program to qualify suppliers, including evaluation of the supplier's process and testing procedures. The manufacturer must have appropriate written specifications for raw materials and packaging, including in-process materials. For material received, the manufacturer must perform at least one appropriate identity test and review the supplier's Certificate of Analysis and other data as appropriate. The manufacturer must have a procedure for verifying all the supplier's test results at appropriate intervals.

Production Process. The manufacturer must develop and maintain data that demonstrates that equipment is suitable and the production process consistently delivers expected results. The latter may be accomplished using statistical process control techniques or other appropriate statistical tools. Master and batch records for every product must be maintained. The process must include the verification of the identity and weight of the ingredients added, and a calculation of yields. The process may also include specific in-process tests appropriate to specifications for unit operations. All activities associated with the production process, including the maintenance, cleaning and calibration of production equipment, as well as all associated QA/QC activities, must be documented in written SOPs, and performed by appropriately qualified and trained individuals.

Finished Product Analysis. There must be appropriate written specifications for finished product, and representative testing of chemical, physical, and

microbiological parameters based on an appropriate statistical sampling plan for the individual product.

A qualified production process of the type outlined above will sharply reduce redundancy in testing as between manufacturers and suppliers, and will ensure a consistency in production that will be more effective and efficient than testing of every finished batch.

B. GRAS Notification – Proposed Section 111.35(d)

In the preamble discussing proposed section 111.35(d), FDA appears to limit the utility of the GRAS notification process. The results of the GRAS notification process have generally been viewed by manufacturers as evidence that a supplier's GRAS determination can be relied upon. FDA now implies that a manufacturer cannot rely on its supplier's GRAS determination, even if FDA itself did not object to that determination.

FDA's position on this issue needlessly introduces uncertainty into the GRAS status of many non-dietary ingredient components in dietary supplements. Moreover, it could well result in multiple, duplicate GRAS notifications being submitted to FDA by industry, which would be an inefficient and unnecessary expenditure of time and resources both by industry and by FDA.

We accept that manufacturers must assure themselves that non-dietary ingredient components of dietary supplements are GRAS, unless they are food or color additives or are authorized by prior sanction. In many cases, manufacturers look to their suppliers to provide guidance on the question as to whether an ingredient is GRAS. In this context, the fact that FDA has not objected to a GRAS notification for that substance is very useful information and provides a manufacturer with a certain assurance that FDA will not object to its use of that substance in a dietary supplement if its use is consistent with the GRAS notification.

FDA does not explain how its position on GRAS notifications promotes the primary purpose of these regulations as identified by FDA: protecting consumers from adulterated and misbranded product. In fact, it will have no meaningful impact on consumer protection, but will merely subject manufacturers to additional costs and uncertainties, and will burden the agency with additional, duplicative GRAS notifications. Shaklee strongly urges FDA to recognize that manufacturers may rely on the results of third-party GRAS notifications in determining whether a substance is GRAS.

II. Other Issues

In addition to the key concerns outlined above, there are a number of other areas where further clarification or amendment of the proposed regulations is needed.

A. Testing Water Supply – Proposed Section 111.15(d)(3)

This section would require manufacturers to maintain documentation or otherwise be able to show that the water used in the manufacture of dietary supplements meets the requirements of the regulation. There has been speculation that this section would require manufacturers to conduct testing of the water at each facility. However, at the West Coast public meeting to discuss the proposed cGMPs held on May 6, 2003, FDA officials stated that a certificate from the local water company providing the water to a facility would be sufficient documentation to satisfy this section's requirement.

Reliance on a certificate from the local water company should be sufficient to satisfy the requirement or proposed section 111.15(d)(3), and this should be confirmed either in the regulation itself or in the preamble to the final regulations.

B. Physical Plant Requirements – Proposed Section 111.20(d)(1)

This section states that the floors, walls, and ceilings of any physical plant used in the manufacture, packaging, or holding of dietary supplements be made of "smooth and hard surfaces." If the requirement is read literally, it could be interpreted to prohibit the use of ceilings with drop-in tiles. While there may be areas in a manufacturing plant where drop-in ceilings are inappropriate given the height of the ceiling, the nature of the product, and/or the type of operation conducted in that area, they are perfectly adequate in many areas of a manufacturing facility, and certainly are appropriate in places where product is labeled or stored. Replacing such ceilings with surfaces that are "smooth and hard" is both costly and unnecessary and would impose significant costs on Shaklee and other manufacturers of dietary supplements.

The overall purpose of this section is to ensure that facilities can be kept in a clean and sanitary condition. We recommend that this section require that physical plants have surfaces that can be adequately cleaned, but give manufacturers the flexibility to use appropriate surfaces in different parts of a plant. Therefore, we suggest that the phrase "that are of smooth and hard surfaces" be deleted from this section, so that the provision says that "the design and construction must include . . . floors, walls, and ceilings that can be adequately cleaned and kept clean and in good repair."

C. Quality Control Function – Proposed Section 111.37

This section appears to require a manufacturer to establish an identified quality control unit that is responsible for all of the quality control activities set out in the cGMPs. Shaklee has a quality control unit, but a number of the activities described in the cGMPs are carried out by personnel in other management groups. At the West Coast public meeting to discuss the proposed cGMPs held on May 6, 2003, FDA officials stated that any individual carrying out a quality control function would be deemed to be part of a