McNeil
Nutritionals

August 8, 2003

Dockets Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

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

Dear Sir or Madam:

McNeil Nutritionals submits the enclosed comments in response to FDA's March 13, 2003, Federal Register notice (FR 68: No. 49, pp 12158-12263) proposing current good manufacturing practice (CGMP) regulations for dietary ingredients and dietary supplements.

McNeil markets three dietary supplement products (Lactaid® Caplets/ Ultrachewables, Viactiv® Calcium Chews, and Benecol® Soft Gels) and, thus, has a vested interest in the development of regulations affecting the manufacture and control of these products.

While, in general, McNeil agrees that the production of dietary ingredients and dietary supplements should be governed by a set of good manufacturing practice regulations, we believe that the FDA proposal goes far beyond what is necessary and far beyond FDA's mandate under DSHEA. In at least one respect, concerning access to records, the proposed CGMPs even exceed drug GMPs.

After reviewing the preamble to the proposed rule, it seems that the agency views the entire dietary ingredient and dietary supplement industry as lacking adequate testing and controls. We agree that there is a sub-set of dietary ingredients and dietary supplements, specifically those derived from botanical and animal sources, for which a higher degree of control may be necessary. However, we disagree with FDA's view that a burdensome set of GMP regulations is necessarily the only remedy for all supplement manufacturers. Other means can be put into place to provide the assurances of identity, strength, quality, and composition for these products that FDA hopes to achieve. For example, guidelines can be put into place to assist companies in improving the manufacture and control of their products. Greater reliance on compendial specifications for botanically derived ingredients is another mechanism that can be used to improve compliance and ensure uniform suitability for use.

More importantly, we disagree that the proposed regulations are necessary for a large segment of the supplement industry whose products are not derived from botanical and animal sources. For these companies, we believe that adherence to the current food GMPs would provide sufficient control.

Our specific comments on elements of the proposed regulation follow:

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Ingredient and finished product testing:

McNeil disagrees with the provisions that would require each component in a dietary ingredient or dietary supplement to be tested. Likewise, we disagree that each batch of finished goods needs to undergo testing. We believe that alternative approaches to ensure label compliance should be acceptable under any final CGMPs.

The "actives" in the McNeil Nutritionals supplement products consist of lactase enzyme (Lactaid® Brand Caplets and Ultrachewables); plant stanol ester (Benecol® Brand Softgels); and calcium carbonate, vitamins D and K (Viactiv® Brand Calcium Chews). Currently, McNeil accepts these "actives" based upon a certificate of analysis provided by the supplier with each shipment. Finished product testing is done periodically to confirm adherence to established specifications. Under the FDA proposal, acceptance of analysis certificates would appear to have little or no value. Rather, each lot of dietary ingredient and/or finished product must be tested in accordance with established specifications.

While section 402 (g)(2) of the DSHEA statute prompts FDA to develop dietary supplement CGMPs, it stipulates that "such regulations shall be modeled after current good manufacturing practice regulations for food..."

Under the current food GMPs (21 CFR §110), manufacturers are permitted to accept certificates of analysis for many types of ingredients, including vitamins and minerals used in conventional foods. Under the system McNeil employs, we audit the supplier's manufacturing process and also review documentation verifying the supplier's process capability. Once a supplier is approved, we do not test each shipment of the dietary ingredient or component. However, an audit-testing program is put in place to verify compliance with the ingredient's specification. In many cases this verification occurs on a once/month or once/quarter frequency, depending on the ingredient's complexity.

Clearly, conventional food manufacturers, who daily incorporate a broad variety of both common and specialized ingredients into their products are allowed to accept these raw materials on the basis of certificates of analysis from the ingredient suppliers, with periodic confirmatory analysis. Many of these ingredients may even be compendial grade (e.g., FCC, NF, and JECFA, etc.) In our view, such a system of periodic testing should be allowed to continue to be acceptable, especially for those dietary ingredients and dietary supplements not derived from sources inherently subject to the variability resulting from climactic changes, growing conditions, pesticides, soil contaminants, cultivars, etc.

Similar logic should apply for finished product testing. The concept of statistical process control has been in place in manufacturing environments for many years, and has proven to be very effective in assuring compliance to specifications, without the burden of testing every batch or component. In employing statistical process control, we enlist the expertise of Engineering, R&D, Operations and Quality Assurance to evaluate the materials and process for manufacturing the end product. Extensive testing is done using statistical sampling plans to understand the inherent variability in the components. The same disciplined approach is used to review the equipment and ultimately the entire process.

Once the appropriate data are collected, both specifications and the standard operating procedure for manufacturing can be developed. This step is followed by random sampling on a monthly or quarterly basis to test finished product for compliance. Routine QA testing during the manufacturing process will also be conducted. Batch data are reviewed daily to ensure all parameters are met prior to release of the finished product. Whenever a deviation occurs, QA has responsibility to review why it occurred and provides recommendations for corrective actions.

This SPC/Six Sigma process is embraced by many industries, many of which require strict compliance to specifications for safety purposes (aircraft manufacturing, automobiles, foods, etc.) It would seem reasonable that this same approach could continue be used in the manufacturing of dietary supplements that are not derived from botanical or animal sources. If a manufacturer uses such an approach over testing each finished batch, it should be their responsibility to document that sound statistical practices have been followed.

It is our view that the dietary ingredient and dietary supplement rules appear to model drug CGMPS more than the food CGMPS. In particular, we believe that the requirements for dietary ingredients and dietary supplements not derived from botanical and animal sources are unnecessarily burdensome. Our experience demonstrates that the procedures we now have in place are entirely sufficient for the manufacture and control of the dietary supplements we market. For example, the analytical data gathered from six-quarters of periodic finished product testing of our calcium supplement show that the product has continually met established specifications. Thus, we question how this product would have been any better controlled had the proposed GMP rules been in effect during that time.

Availability of records for photocopying and sample retention:

We object to the requirement that all records to be retained under the proposed rule must be made available for photocopying by FDA upon request. FDA's proposed access to manufacturing records in the dietary supplement and related foods industry is unprecedented. While certain limited circumstances exist in which FDA has access to manufacturing records (production records for low acid canned foods and the one-up/one-down shipment records specifically authorized under the Bioterrorism Act), FDA has generally been denied records access to food facilities. DHSEA mandates that dietary supplements be viewed as foods (except for certain labeling provisions under section 201(g)), whereas the FDA's attempt here is to gain record access to the level and degree of that is, generally, not even afforded during FDA drug inspections. Clearly, this level and degree of general records access is not authorized by the DSHEA statute, and may infringe a company's right to maintain the confidentiality of proprietary information.

Under the proposed rule, FDA mandates that samples of all finished products be collected and held for three years. FDA provides no insight on how it arrived at a three-year hold time, nor any guidance on how these samples are to be held. Even if maintained under what would be typical storage conditions for the product, what value would there be in holding for three years a product that may have a shelf life of one-year? If the product were to degrade after one-year, what useful information would be gained by keeping it for two more years? To hold product samples beyond their expected shelf life, especially if they degrade, could potentially expose the company to litigation. We propose that samples be retained only for the shelf life of the product.

Associated costs:

In reviewing the costs that would be associated with the testing of one of our products under the proposed rule, we believe that FDA has vastly underestimated expenditures for compliance. We calculate that the annualized costs alone for finished product testing of vitamins D and K, and calcium carbonate in our calcium supplement would approach $120,000 per year. (Consider what these costs would be for a manufacturer producing a multi-vitamin/mineral product with 20 or more components.) Having to also conduct testing on incoming components would significantly increase these costs. We would also anticipate incurring additional carrying costs for finished goods that have to be held until finished product testing is completed.

Added to this would be costs (personnel, space, and equipment, etc.) associated with other compliance requirements mandated by the proposed rule, e.g., establishing and validating calibration and cleaning SOPs, enhancing label control processes, collecting and retaining samples, developing and validating test methods, maintaining records of all consumer complaints. Although we currently perform these functions, it is with considerably less "formality" than is prescribed by the proposed regulation. In light of our experience with the products we market, we question the benefit of adding complexity to a system that already works.

The significant record keeping requirements proposed also would translate into additional costs associated with creating and maintaining (for three-years) the records specified under the rule. As noted above, these requirements go far beyond the CGMPs for food, upon which FDA's statutory mandate for dietary supplement and dietary ingredient GMPs is based.

While some of the costs associated with compliance under the proposed rule might be decreased if the all component and finished product testing were brought in-house, doing so would incur capital investment for space and equipment, as well as the costs associated with hiring, training, and maintaining additional personnel.

Dietary Ingredients/GRAS Ingredients

In reviewing the proposed regulation, it appears that FDA is attempting to maintain some food additive authority for dietary supplements, even though they are excluded from the food additive definition, as stipulated in section 3(b) of the Dietary Supplement Health and Education Act (DSHEA), and codified under 402(s) of the Federal Food, Drug, and Cosmetic Act. An article marketed as a dietary supplement, including its components that constitute the article, also are excluded from this definition. This attempt by the FDA to subsume dietary supplements under the food additive definition clearly circumvents Congressional intent promulgated in DSHEA. Furthermore, the definition of a dietary supplement under 201(ff)(1) is sufficiently broad to include the use of any ingredient in an article marketed as a dietary supplement. FDA should rescind 21 CFR § 111.35(d) as proposed because of this exclusion under DSHEA. By the same premise, caffeine present in foods would be regulated as an OTC stimulant. Components should be regulated based on intended use of the finished product.

We are puzzled by FDA's intent relative to GRAS ingredients that are used as components of dietary supplements. Proposed 21 CFR §111.35(d) would require that all of the non-dietary ingredient components be (a) approved food additives, (b) authorized by prior sanctioning, (c) a color additive, specifically permitted for use in supplements, or (d) a GRAS ingredient. Under the rule, the agency would require that any component claimed as GRAS would have to be supported in the manufacturers files by either reference to an FDA regulation or by an explanation as to the basis of general recognition of safety for use of the substance in the supplement. Moreover, the preamble to the proposed rule explains that supplement manufacturers may not rely on the conclusions of their suppliers as to the GRAS status of ingredients used as components or on agency response letters to GRAS Notifications. Rather, each manufacturer would be required to create a file that establishes the basis of its determination for each component it concludes is GRAS.

Essentially, this requirement undermines the utility of the GRAS notification process that was established in 1997 and welcomed by ingredient companies and their customers. Under the proposed 1997 GRAS rule, ingredient suppliers finally had a workable mechanism with which to demonstrate FDA corroboration of their GRAS self-affirmations to prospective customers. Now, under proposed 21 CFR §111.35(d), there is considerable potential that many of the ingredients used in dietary supplements could be subjected to the food additive

process. We believe that FDA should allow dietary supplement companies to use GRAS Notification letters in the same manner that conventional food manufacturers do. (Unless this current proposal represents FDA's first salvo in an effort to do away with the GRAS process altogether.)

To require each dietary supplement company to maintain a similar determination as to the GRAS status of a particular ingredient is duplicative and wasteful.

Summary:

We agree that the articles regulated by FDA should be subject to a set of GMPs, provided that the rules are commensurate with the level of control needed to ensure that the finished products meet certain standards. In proposing the dietary ingredient and dietary supplement GMPs, FDA asserted that it was proposing the rules as "minimum" requirements. However, we believe that, in many respects, the agency went well beyond the minimum necessary to provide adequate control, especially for the substantial segment of dietary ingredient and dietary supplement producers whose products do not contain "actives" derived from botanical and animal sources.

Instead of using a blanket approach to regulating the manufacture of all dietary ingredients and dietary supplements, other options are available. We propose that those dietary ingredients and dietary supplements that are not subject to environmental conditions be governed by the current food GMPs as set forth in 21 CFR §110. For those products derived from plant and animal sources that are subject to environmental variation and, thus, a greater compliance challenge, FDA could apply stricter requirements with respect to component and/or finished product testing. FDA could accomplish this by establishing manufacturing and control guidelines for these products or through specialized GMPs.

There is precedence for special GMP requirements for certain food product categories, given the manner in which FDA currently regulates thermally processed low acid canned foods, acidified foods, juice, and seafood. The benefit of using a focused approach would be that a large percentage of the currently marketed dietary supplements could immediately be made subject to the current food GMPs in 21 CFR §110. FDA could then concentrate its resources on establishing either specialized GMP requirements or manufacturing and control guidelines for botanical and animal sourced products. In this way, FDA would be concentrating its resources on the sub-set of products with the most potential for compliance challenges, instead of applying unnecessary rules to the entire supplement industry. For many in this industry, the proposed rules, if enacted as is, would mean considerably more expenditures without necessarily improving product quality.

We appreciate the opportunity to comment on this proposal and trust that our comments will be useful.

Sincerely,

Richard Reo

Richard Reo
Director, Regulatory Affairs