NATIONAL
ENZYME
COMPANY

August 8, 2003

Via Electronic Transmission @ http://www.fda.gov/dockets/ecomments

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

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

Dear Sir or Madam:

National Enzyme Company respectfully submits these comments to the Food and Drug Administration's ("FDA") proposed rule entitled, "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements" ("proposed rule") which was published in the Federal Register on March 13, 2003. 68 Fed. Reg. 12158.

National Enzyme Company (NEC) is a dietary supplement contract manufacturer, in business since 1932, which meets the criteria for "small establishments" per FDA's definition. NEC maintains a quality control unit and an in-house laboratory, and has the systems and specifications in place which are modeled to comply with both the Advance Notice of Proposed Rulemaking (ANPR per 62FR5700) and the National Nutritional Foods Association's Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements. In addition, National Enzyme Company holds a facility GMP certification from NSF. We believe our current level of cGMP commitment offers National Enzyme Company a worthwhile perspective from which to provide commentary to the proposals contained in docket number 96N-0417.

National Enzyme Company commends the FDA on this effort to ensure consumers' access to safe dietary supplements, and supports this effort to codify cGMP's for the industry. As a responsible manufacturer of dietary supplements, we welcome the potential benefits of increased consumer confidence, and a level playing field where all firms must manufacture and sell un-adulterated products.

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There are, however, some aspects of the proposed regulation which appear overly burdensome and economically unfeasible for small manufacturing entities such as ours. In particular, there are proposed production and process control requirements which seem redundant, and unnecessarily complicate existing good manufacturing standards of practice with little or no improvement to product safety and quality. These concerns are outlined below

I. Legal Authority Within the Scope of DSHEA Statutory Mandate

To begin, National Enzyme Company respectfully requests that FDA reconsider the scope of the proposed CGMP rule, particularly with regard to the proposed requirements for production and process controls. Under DSHEA, Congress granted FDA authority to "prescribe good manufacturing practices for dietary supplements." DSHEA § 9; FDC Act § 402(g)(2). However, the legislation clearly circumscribed the scope of any GMP regulation by specifically stating, "such regulations shall be modeled after current good manufacturing practices regulations for food and may not impose standards for which there is no current and generally available analytical methodology." We believe the intent of this provision is clear. Congress did not want FDA to regulate dietary supplement good manufacturing practices in the same manner it regulates drug good manufacturing practices.

National Enzyme Company recognizes that dietary supplement CGMPs need to include additional provisions related to identity, purity, strength, quality, and composition, but questions the overly burdensome methods FDA has proposed for assuring these properties, particularly with respect to the production and process controls. The following sections address those provisions in particular...

II. Proposed Subsection E, Production and Process Controls, Would Impose Unnecessary and Overly Burdensome Requirements on the Dietary Supplement Industry With Little Gain to Product Safety and Quality

1. Proposed § 111.35(d)(4)

This section would require that any substance, other than a dietary ingredient, be an approved food additive, authorized by a prior sanction, or GRAS "for use in a dietary ingredient or dietary supplement." According to the preamble discussion, FDA appears to envision that companies will document the rationale supporting the use of each non-dietary ingredient in their supplements. 68 Fed. Reg. at 12195-96.

National Enzyme Company believes this requirement is unnecessary and would be overly burdensome since many of the substances likely to be used as "other ingredients" are generally recognized as safe ("GRAS") for broad food use. Historically firms have used food items or additives (food grade or GRAS materials) in their products. Under this section, it seems that some traditional ingredients that have been used appropriately in the past under DSHEA could not be used in a dietary supplement or a dietary ingredient if they do not have a GRAS status that specifically includes those two uses. This rule, as it is written, would limit the availability of products to the consumer, including products they are already using. National Enzyme Company can discern no real or perceived consumer benefit of this requirement, especially considering the redundancy of performing a GRAS application of an ingredient for use in a product which typically offers a lower level of consumer exposure than existing food uses.

2. Proposed § 111.35(g)(1)-(2)

This section would require that companies "test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met . . ." For any specification that cannot be tested on the finished batch, companies must "perform testing on each shipment lot of components, dietary ingredients, or dietary supplements received . . . and . . . perform testing in-process . . . ."

National Enzyme Company believes this testing requirement is overly burdensome, particularly in the context of the preamble discussion (where it seems companies cannot use vendor certificates of analysis in lieu of on site testing, and that skip-lot analysis is not allowed. 68 Fed. Reg. at 12198). We are puzzled why FDA would disallow the use of these well-proven quality assurance techniques such as vendor qualification, and impose requirements that far exceed the requirements in other food and drug regulations. For example, in drug regulation 21 C.F.R. § 211.165(a), it states, "for each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release." (Emphasis added.) The drug CGMP regulations do not require the determination of the identity, purity, quality, strength or composition of "other ingredients" such as excipients in a final drug product. In contrast, the proposed dietary supplement CGMPs would require testing of these non-dietary ingredients. Similarly, reliance on certificates of analysis and skip-lot testing are clearly allowed in the drug industry.

National Enzyme Company believes the focus on testing in the CGMP rule will impose major and unnecessary costs on many suppliers of dietary ingredients and supplement manufacturers who already have well-controlled processes in place. Currently most companies purchase their ingredients from firms that have been approved as suppliers of the ingredients. Firms then often regularly use certificates of analysis from these approved suppliers as a guarantee of many quality points of the raw materials. Each incoming batch or container may be sampled and identified, but it is redundant and economically not feasible to perform the full regimen of analyses on all incoming lots. A quality system of vendor certification and skip-lot analyses serves the drug industry well, it seems the innocuous nature of most dietary supplement products warrants no greater level of testing requirements.

3. Proposed § 111.35(h)

This section would require that companies use appropriate tests to determine whether its specifications are met. National Enzyme Company is concerned that this provision could be interpreted as requiring companies to test dietary ingredients and supplements for not only compliance with the company's specifications, but also for compliance with any labeled specifications met by the ingredient suppliers, e.g., levels of aflatoxins, heavy metals, lead, etc. This would be redundant and overly burdensome. NEC requests that FDA reconsider this requirement or clarify that revalidation is not necessary. See also related comments at item 7 concerning proposed § 111.60.

4. Proposed §§ 111.35(i)(4)(iii) and 111.50(f)

Section 111.35(i)(4)(iii) would prohibit the reprocessing of any component, dietary ingredient, or dietary supplement "because of contamination with microorganisms or other contaminants, such as heavy metals." Section 111.50(f) (concerning batch production records) states this prohibition differently. The latter 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." (Emphasis added.)

National Enzyme Company is concerned that the reprocessing prohibition, particularly as stated in § 111.35(i)(4), is overly stringent and directly at odds with FDA's food regulations. Of most significance is the apparent inconsistency between proposed § 111.35(i)(4) and FDA's food additive regulation which specifically authorizes the use of ionizing radiation to treat food for microbial disinfection and food-borne pathogens. NEC requests clarification of FDA's intent. There is, of course, a large difference between contamination with any microorganism and with microorganisms of public health significance.

Furthermore, with respect to the reprocessing prohibition, FDA justifies this provision in the preamble discussion by stating that reprocessing cannot effectively eliminate such forms of contamination without adversely affecting the component, dietary ingredient, or dietary supplement. 68 Fed. Reg. at 12199. We would again disagree and note that many dietary supplement components and ingredients are accepted for use in food products and might, as such, have been subject to reprocessing because of prior contamination.

It is unclear to National Enzyme Company why such reprocessing is acceptable for food ingredients, but is not allowable for dietary components, ingredients, or supplements. Keeping in mind that many of the components in dietary supplements are purchased as food ingredients, it is especially possible that microbiological counts of such ingredients could surpass those typically required by a manufacturer of a dietary supplement. This puts some firms – particularly suppliers of dietary ingredients – in a precarious situation because they may not be able to purchase food ingredients with the limits that are acceptable to their customers who make dietary supplements. In these cases it is not uncommon for the ingredients to be treated to obtain a lower microbiological count. The processes used are currently approved for food items (by category) but would not be allowed by this proposed rule. This is especially burdensome to companies who supply plant and herbal products that often have high microbiological counts. National Enzyme Company believes reprocessing steps that are currently deemed safe and allowed for food items should likewise be allowed for dietary ingredients.

5. Proposed § 111.35(m)

This section would require that the results of all testing and examinations on a batch production appear in the batch production record. National Enzyme Company is concerned that this requirement, in conjunction with the specific batch production record requirements of § 111.50(c), creates unnecessary and duplicative record keeping requirements.

For example, this provision appears to require that all relevant cleaning and equipment calibration records be included in each batch record, but the same records could apply to multiple batches in the same day or period of time. Current practice is to include this information in log books – one central record – that would be referenced in the batch records. The use of log books instead of including such information in every batch record would eliminate a great deal of paperwork and provide exactly the same valuable information. There seems to be no logical reason to include highly repetitive information in every batch record.

6. Proposed § 111.45

This section would require that a master manufacturing record be prepared for each product made and each batch size. National Enzyme Company believes the inclusion of the batch size provision is overly burdensome, especially to smaller firms who specialize in custom blended or custom made products. As currently written, it appears that firms are not allowed to produce one master manufacturing record for a product (given by percentage by weight or for one set batch size) and just reference scale-up by simple mathematics.

National Enzyme Company questions why it would not be acceptable to simply give a formula for a product in the master manufacturing record and then give directions for adjusting the weights of ingredients depending on the amount of product that is to be produced. The individual batch records could then include the actual amounts of the ingredients used per the scale-up or scale-down directions from the master manufacturing record. There seems to be no purpose to requiring a separate master record for each batch size available.

This overly burdensome proposal will certainly affect the flexibility of smaller firms who regularly adapt batch size to fit each individual customer's needs. The end result of this may be to force manufacturers to produce their items in batches of specific standard sizes in order to avoid additional paperwork and, perhaps, personnel. NEC can discern no real or perceived benefit to the consumer for this provision.

7. Proposed § 111.60(a) and § 111.60(b)(v)

Section 111.60(a) would require companies to use adequate laboratory facilities "to perform whatever testing and examinations are necessary to determine that components, dietary ingredients, and dietary supplements received meet specifications; that specifications are met during in-process, as specified in the master manufacturing record; and that dietary ingredients and dietary supplements manufactured meet specifications." This section would also require that each dietary ingredient or dietary supplement batch manufactured be tested "to determine that the dietary ingredient or dietary supplement meets specifications."

As written, it appears to require a company to test each batch of dietary ingredient or dietary supplement manufactured for compliance with every specification carried over from an ingredient supplier. Please see comments offered on section 3. regarding Proposed § 111.35(h). Additionally, National Enzyme Company requests clarification of the proposed requirement in § 111.60(b)(v) that a firm make "use of appropriate test method validations." It appears that FDA expects companies to validate that official or nonofficial test methods used in the production of dietary ingredients and dietary supplements work under the specific conditions of use present in the manufacturing facility. See discussion on pages 12208-09. This would require companies to revalidate methods already recognized as official standards, such as USP and AOAC references. NEC would suggest that the word "validate" be changed to "verify", especially in the case of validated compendia "official" methods. Otherwise, we do not understand the scientific rationale behind asking companies to perform a full validation on procedures that have already undergone rigorous examination and public comment in order to be "official methods", keeping in mind that inter-laboratory studies are included in the original validation.

8. Expiration Dating

National Enzyme Company supports excluding specific criteria for expiration dating of products. The range of dietary supplements and ingredients currently available is extremely wide and it would be very difficult to impose relevant expiration dating regulations on such a wide variety of items. NEC believes that it should be the responsibility of dietary supplement manufacturers to determine when expiration dates are appropriate and what dates are appropriate given the studies they have performed on their own products. As long as the dietary supplement manufacturer is required to have appropriate data to support the expiration date(s) chosen, we see no need to include further regulations regarding the date.

III. FDA's Cost Estimate of the Economic Impact

National Enzyme Company believes the FDA has grossly underestimated the financial impact of the proposed CGMP rule. In particular, small firms which utilize enzymes in dietary supplements will be faced with significant economic challenges should the proposed rule stand. As evidence, we have provided "real-world" estimates of testing costs. Testing cost estimates are focused on here because (a) conscientious dietary supplement manufacturers will incur fewer extra costs for general GMP compliance activities (sanitation, production & process controls, holding & distributing, consumer complaints), while (b) the testing cost estimates calculated by the FDA on page 12240 of the docket are grossly inaccurate. Clearly, testing costs will represent the most significant economic burden for small manufacturers.

To calculate the impact on finished product testing, we have calculated our own internal actual testing costs for each dietary supplement ingredient (potency/ identification/ defects) to be approximately $300 per ingredient. We further calculated our own average number of ingredients per batch is 8. Using FDA's numbers for annual small entity batches produced (554), we calculate the finished product testing cost of enzyme containing dietary supplements to exceed $1.3 million annually. This does not include potential method development requirements. This figure contrasts sharply with FDA's calculation of *total costs* of $99,000 the 1st year and $61,000 each year after.

The small entity dietary supplement manufacturer may also approach the proposed CGMP rule through exhaustive raw material ingredient testing. This approach will be required in many cases where finished product testing is impractical for analytical reasons. Using FDA's own estimate of 6.5 batches of finished-product per ingredient lot, we calculate an average of 682 ingredient shipments annually (554 production batches x 8 ingredients ÷ 6.5 batches per ingredient). At our actual figure of $300 testing costs per ingredient, we can expect to spend $204,600 annually to test each incoming enzyme ingredient. This estimate does not include excipient or component testing, in-process testing and controls, etc. Again, this figure (representing incoming raw material testing alone) is significantly greater than the FDA's estimated *total costs* for small firms of $99,000 the 1st year and $61,000 each year after.

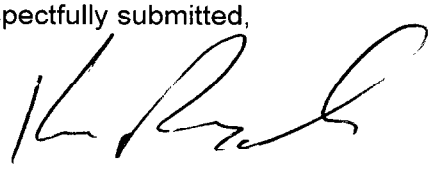
Clearly then, the cost/ benefit figures offered in Table 18 (pg. 12243) are inaccurate and unrepresentative of the likely financial impact of the proposed rule. The primary weakness in FDA's analysis comes from the agency's misestimates of testing cost and its failure to consider the increase in testing that would be necessary due to the proposed disallowance of certificates of analysis throughout the supply chain.

IV. Conclusion

In sum, National Enzyme Company supports FDA's efforts in establishing a CGMP regulation for dietary supplements. However, NEC remains concerned about the scope of the proposed rule and the above enumerated provisions in the Production and Process Controls section which appear redundant, costly, and would unnecessarily complicate existing good manufacturing practices with little improvement to consumer safety or product quality.

National Enzyme Company appreciates the opportunity to provide comments on the proposed CGMP rule.

Respectfully submitted,



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