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Via Electronic Transmission and Federal Express

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:

The Enzyme Technical Association ("ETA") 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 (to be codified at 21 C.F.R. parts 111, 112). On April 24, 2003, ETA submitted initial comments to the proposed rule that were limited in scope to FDA's proposed time period for submitting comments.[1] With this submission, ETA provides additional comments on substantive aspects of the proposed rule.

ETA is a trade association of companies that represent manufacturers and distributors of enzyme preparations in the United States, Canada, and Mexico. Since its establishment in 1970, ETA has taken an active role in assisting in the development of regulations and policies that affect the enzyme industry. Its membership represents a majority of the North American enzyme industry.

Because enzymes may be incorporated in dietary supplement products, ETA is interested in the terms and scope of the proposed rule. Enzymes are proteins with highly specialized catalytic functions. They are responsible for all metabolic processes. Like all other proteins, enzymes are composed of amino acids, however, they differ in function in that they have the unique ability to facilitate biochemical reactions without undergoing change themselves. As a result, enzymes are highly efficient catalysts in biochemical reactions, that is, they help a chemical

[1] In response to this request and similar requests from multiple other parties, FDA extended the comment period to August 11, 2003. 68 Fed. Reg. 27008 (May 19, 2003).

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reaction take place quickly and efficiently. Enzymes play a diversified role in many aspects of daily life, the most salient for purposes of these comments are their role in the production of food and dietary supplements and as a dietary ingredient that facilitates digestion.

ETA commends FDA on this effort to ensure consumers' access to safe dietary supplements and supports this goal. However, as expressed more fully below, ETA believes the CGMPs, as proposed, are overly burdensome and at odds with the statutory mandate of the Dietary Supplement Health and Education Act of 1994 ("DSHEA").[2] ETA is also concerned that many of the proposed production and process control requirements are redundant and unnecessarily complicate existing good manufacturing standards of practice with little or no improvement to product safety and quality.

I. ACTION REQUESTED

ETA respectfully requests that FDA reconsider the scope of the proposed CGMP rule, particularly with regard to the proposed requirements for production and process controls. As currently proposed, ETA believes FDA, in many places, is requiring dietary supplement manufacturers and ingredient suppliers to meet more stringent requirements than exist for drug products. As currently written, the proposed requirements would place a heavy burden on the dietary supplement industry with little, if any, increase in consumer safety or product quality as compared to existing practices.

II. DISCUSSION

In issuing the proposed rule on dietary supplement CGMPs, FDA asked for comments on a number of aspects of the proposed rule including:

- "The depth and breadth of what should be considered by the agency in developing the final rule."
- "Whether each of the proposed provisions are necessary to ensure the safety and quality of dietary ingredients and dietary supplements and whether they are adequate to protect the public health."
- "Whether the gains to consumers in product safety and quality are warranted."

68 Fed. Reg. at 12161.

ETA addresses these three items in the context of its comments to the proposed rule. To summarize, ETA is concerned that, as currently proposed, the dietary supplement CGMPs are overly burdensome and unduly complicate certain aspects of good manufacturing practice.

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[2] Pub. L. No. 103-417, 108 Stat. 4325 (2000) (codified throughout 21 U.S.C.).

Specifically, ETA is concerned that: (1) the proposed rule is not consistent with the statutory mandate that it be modeled after the food CGMPs, and (2) Subsection E, Production and Process Controls, would impose redundant, costly and unnecessary requirements on dietary supplement manufacturers and ingredient suppliers with little if any gain to product safety and quality. Each of these comments is discussed in greater detail below.

A. The Proposed Rule for Dietary Supplement CGMPs is Inconsistent with the Statutory Mandate that Such Regulations be Modeled After the Food CGMPs

Under DSHEA, Congress granted FDA authority to "prescribe good manufacturing practices for dietary supplements." DSHEA § 9; 21 U.S.C. § 342(g)(2) (2000). 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." Id.

ETA believes 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. FDA, in its preamble to the proposed rule, goes through a tortuous discussion to support the proposition that by using the term "modeled after," Congress intended the food CGMPS as only a "model" or "preliminary pattern" for the dietary supplement CGMPs. As further support, FDA states, "If Congress had intended for the agency to adopt food CGMPs . . . Congress could have explicitly stated that dietary supplements were subject to food CGMPs." 68 Fed. Reg. at 12165. ETA does not find this argument persuasive and posits that Congress clearly intended dietary supplements to be subject to food CGMPs, as evidenced by the explicit definition of dietary supplements as "food within the meaning of this Act." DSHEA § 3(a), 21 U.S.C. § 321(ff).

Rather, ETA believes FDA should more appropriately turn to the definition of the verb, "modeled" rather than the noun, "model" to determine Congressional intent. According to the FDA cited dictionary, Webster's II New Riverside University Dictionary, "modeled" is defined as, "to make conform to a selected standard." Thus, when Congress used the term, "shall be modeled after" it intended that any dietary supplement CGMP regulations issued would conform to the food CGMP, with only occasional deviation from those standards. Clearly, Congress did not envision standards as strict as, if not stricter than, those which currently exist for drug products.

ETA does not disagree with FDA 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. See discussion below.

B. 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.

ETA believes such a 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. Not only would the rule, as it is written, limit the availability of products to the consumer (products they are already using), but some firms could literally be put out of business because they have been relying on the use of food products in their process. ETA believes that this puts some firms at a disadvantage, especially smaller firms that do not have a regulatory department that can specifically deal with GRAS petitions / notices.

It is also important to remember that many dietary ingredients are currently sourced from companies that are manufacturers of food ingredients and food additives. For most of these food ingredients / additives companies, selling items that will eventually be called dietary ingredients is a relatively small portion of their business. It is unlikely that many of these companies will be willing to engage in a GRAS review in order to accommodate the relatively small dietary ingredients market.

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 . . . ."

ETA believes this testing requirement is overly burdensome, particularly since, according to the preamble discussion, it seems that companies cannot use vendor certificates of analysis in lieu of on site testing and that skip-lot analysis is not allowed. See 68 Fed. Reg. at 12198. We are puzzled why FDA would basically disallow the use of these well-proven quality assurance techniques and impose requirements that far exceed the requirements in other food and drug

regulations. For example, drug regulation 21 C.F.R. § 211.165(a) 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.

ETA believes the proposed rule's focus on testing 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 regularly use certificates of analysis from these approved suppliers as a guarantee of the quality of the raw materials, without analysis of all incoming lots of the raw ingredient. The quality is sometimes checked by skip-lot analysis, but most firms lack the equipment and personnel to test every lot of every ingredient every time it is received. While contract laboratories can be used to test these ingredients, the types of analysis required for many dietary ingredients is highly specialized and would be expensive to outsource.

It is unclear to us why FDA is deviating from this standard of practice and proposing a standard much more rigorous than that which exists for drug products. ETA believes that the costs of the required testing, particularly if vendors' certificates of analysis *and* skip-lot testing are not allowed, will be extremely high. For example, if a company typically produces fifteen different products a day and all of the products must be tested for an average of eight different specifications (at an estimated cost of $20 per test, which is an extremely reasonable estimate), then the total cost of analysis for one day's products would be in the range of $2,400. Because we in the enzyme industry typically deal with custom-made items, it is difficult to prepare larger lots to reduce the cost of analysis over time and many tests would need to be sourced out to contract laboratories. In addition, in order to continue to test all of our blended materials (instead of the skip lot analysis we currently use), we would be subject to the cost of added personnel to test and ship samples and coordinate results. The end result would easily be a yearly added cost of testing in the hundreds of thousands of dollars – an exorbitant amount of money for a small ingredients manufacturer.

Separately, ETA requests clarification of what would be considered "in-process" for materials that are simply blended together to form a final product. In the case that the final material cannot be tested for all of the specifications (because of interferences or because no method exists), how would a firm test the in-process samples?

3. Proposed § 111.35(h)

This section would require that companies use appropriate tests to determine whether its specifications are met. ETA 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. ETA 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.)

ETA 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. ETA 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 components and ingredients that are purchased by enzyme manufacturers (as a supplier of dietary ingredients) are food grade products and accepted for use in food products and might, as such, have been subject to reprocessing because of prior contamination (before we purchased the item).

It is unclear to ETA 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. ETA 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. ETA is concerned that this requirement, in conjunction with the specific batch production record requirements of § 111.50(c), creates unnecessary and duplicative recordkeeping 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. ETA 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.

ETA 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.

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."

ETA is concerned that this provision, along with §§ 111.35(g) and (h), would be highly disruptive to the dietary supplement industry and would impose a great burden on companies that traditionally rely on the certification of ingredient suppliers as to compliance with USP, AOAC, JECFA, and other standards. As written, it appears to require a company to test each batch of dietary ingredient or dietary supplement for compliance with every specification carried over from an ingredient supplier.

Separately, ETA 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 68 Fed. Reg. at 12208-09. This would require companies to revalidate methods already recognized as official standards, such as USP and AOAC references. ETA would suggest that the word "validate" be changed to "verify", especially in the case of validated compendial "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. Proposed § 111.70

This section would set specific packaging and labeling controls for dietary ingredients and dietary supplements. ETA is concerned that the proposed requirements are unnecessarily stringent for dietary ingredients since the potential for abuse is primarily at the final product stage.

9. Expiration Dating

ETA 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. ETA 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.

C. FDA's Cost Estimate of the Economic Impact

ETA 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 below an estimate of testing costs alone. The estimates are given for a small enzyme dietary supplement contract manufacturer which will incur little costs for general GMP compliance activities (sanitation, production and process controls, holding and distributing, consumer complaints), but will incur significant testing costs under the proposed dietary supplement CGMP rule.

To calculate the impact on finished product testing, we assumed actual testing costs for enzyme ingredients (potency/ identification/ defects) at $300 per ingredient (a very conservative estimate). We further assumed that the average number of enzyme ingredients per batch is 5. 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 $800,000 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 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 426 ingredient shipments annually (554 production batches x 5 ingredients ÷ 6.5 batches per ingredient). At the conservative estimate of $300 testing costs per enzyme ingredient, we can expect to spend $127,800 annually to test each incoming enzyme ingredient. This estimate does not include non-enzyme ingredient testing, in-process testing and controls, etc. Again, this figure (representing incoming raw material enzyme 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 on Table 18, 68 Fed. Reg. at 12243, are inaccurate and unrepresentative of the likely financial impact of the proposed rule. The primary flaw 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.

III. CONCLUSION

In sum, ETA supports FDA's efforts in establishing a CGMP regulation for dietary supplements. However, ETA 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.

ETA appreciates the opportunity to provide comments on the proposed CGMP rule and welcomes any questions FDA may have on these comments.

Respectfully submitted,

Alice Caddow / ACP

Alice Caddow, Chair
ETA