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VIA ELECTRONIC SUMBISSION
AND FEDERAL EXPRESS

August 6, 2003

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

Re: BASF Corporation's Comments on FDA's Proposed Regulation on Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements (Docket No. 96N-0417)

Dear Sir:

In response to the Food and Drug Administration's (FDA) notice of proposed rule making entitled "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements" BASF Corporation (BC) is respectfully submitting comments. The proposal, which was published in the Federal Register on March 13, 2003 *(68 Fed. Reg. 12157),* implements certain provision of the Dietary Supplement Health and Education Act of 1994 (DSHEA) with regard to the establishment of Current Good Manufacturing Practice (cGMP) for dietary supplements. FDA has requested comments concerning the minimum cGMP necessary to ensure that dietary supplements and dietary ingredients are manufactured, packaged and held in a manner that ensures they are not adulterated or misbranded.

Based in Mt. Olive, New Jersey, BASF Corporation is the North American affiliate of BASF Aktiengesellschaft, Ludwigshafen, Germany. BC's diverse product mix includes chemicals, coatings, plastics, colorants, and health and nutritional products. As part of the health and nutritional product line, dietary ingredients are imported from our foreign affiliates and distributed to domestic manufactures of dietary supplements. In addition, BC's domestic operations include the blending of dietary ingredients received from our affiliates with other dietary components, (excipients such as fillers, binders etc.). These blends are distributed to manufacturers of dietary supplements and are either compressed directly or further processed into a dietary supplement product. Thus, BC as a holder of dietary ingredients and a manufacturer, holder and packer of dietary supplements, is subject to the proposed rule.

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BC supports Congress and the FDA in efforts to ensure that consumers have access to unadulterated and properly labeled dietary supplements. Our commitment to this effort is confirmed by the fact that many of the controls contemplated by the proposal are already in place to ensure that our customers receive product that is safe for the intended use.

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As enacted by Congress, DSHEA instructs FDA to prescribe good manufacturing practice for dietary supplements that are modeled after cGMP for food. BC believes that FDA exceeded Congress's mandate by including dietary ingredients in the cGMP proposal and by proposing requirements similar to, or in some cases more restrictive than, drug cGMP. In doing so, FDA has proposed overly broad and restrictive regulations that place an undue burden on industry without a corresponding benefit to the safety of dietary supplement products and the protection of public health. Our specific concerns follow.

Dietary Ingredients vs. Dietary Supplements

As noted previously, Congress instructed FDA to prescribe good manufacturing practices for "dietary supplements." The definition of a dietary supplement under DSHEA is a product that contains one or more dietary ingredient and is intended for ingestion in tablet, capsule, powder, softgel, gelcap or liquid form. As the definition does not explicitly include the dietary ingredient alone[1], a dietary supplement can only refer to the products containing these ingredients. Thus, Congress instructed FDA to promulgate cGMP regulations for *dietary supplement products* and not for the *dietary ingredients* contained therein. By including dietary ingredients in the cGMP proposal it appears that FDA has broadened the definition of a dietary supplement to an extent that cannot be supported statutorily.

While BC does not believe it was the intent of Congress to require cGMP for the dietary ingredients contained in dietary supplements, we recognize the need to ensure that dietary ingredients are suitable for their intended use and manufactured in a manner to prevent adulteration. However, BC believes that the cGMP requirements as proposed are not readily applicable to the manufacture of dietary ingredients as the processes used for the manufacture of these ingredients differ vastly from those utilized for dietary supplements. Many of the provisions under the proposal are excessive and not applicable to current industry practice when applied to the closed continuous systems used by ingredient manufacturers. Thus, BC believes that dietary ingredients should not be included within the scope of the proposal. There are, however, instances where cGMP for the manufacture of dietary ingredients may parallel the requirements set out in FDA's proposal. Therefore, the proposal can serve as a guide for manufacturers of dietary ingredients until further guidance specifically related to cGMP for the manufacturing, processing or holding of these substances can be issued.[2]

Using the history of drug regulation as a correlation, BC notes that FDA recognized that cGMP for finished pharmaceuticals differed from cGMP for active pharmaceutical ingredients (API) to an extent that excluded API manufacturers from applying the regulation to their operation in a cost effective manner. FDA therefore instructed API manufacturers to use the cGMP regulations for finished pharmaceuticals as a guide until regulations applicable to the manufacture of API's were promulgated. While regulations

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[1] A definition under Section 201(ff) of the FFDCA such as "the term dietary supplement means the following dietary ingredients or a product intended to supplement the diets that bears or contains on or more of the following dietary ingredients..." would be needed to appropriately include dietary ingredients in FDA's proposal.

[2] Reference is made to an outline for a proposed guidance document on cGMP for the manufacture of dietary ingredients submitted by the Counsel for Responsible Nutrition in response to FDA's March 13, 2003 (68 Fed. Reg. 12157) proposal.

have not been promulgated, FDA has issued or adopted other guidance (Q7A) to assist industry with cGMP for the manufacture, processing and holding of API's. BC believes the same approach should be taken with regard to cGMP for dietary ingredients.

Access to Records

BC is concerned that FDA has proposed requirements for access to records that demonstrate compliance with cGMP without the appropriate statutory authority. Proposed Section 111.125(c) requires that all records necessary under the proposal be made available for inspection and copying by FDA. Very detailed and explicit records pertaining to nine broad categories[3] are required under the proposal. While BC believes that records may be necessary to demonstrate that cGMPs are maintained throughout the manufacturing and distribution process, we do not believe that Congress has given FDA the authority to mandate access to these records. FDA has stated in the proposal that it has authority under Section 402(g) of the FFDCA, the adulterated food provisions, to access records that demonstrate compliance with cGMP. BC believes, however, that the statutory provision stating that a dietary supplement is adulterated unless manufactured under cGMP in and of itself does not give FDA the authority to access records required by cGMP regulation. BC believes that explicit authority for record access must be granted such as that seen, for example, with drugs, in the record access authority granted under the new drug provision, Section 505 (k)(2), and the factory inspection provisions for prescription and OTC drugs, Section 704(a). BC further notes that general record access is unprecedented in the food industry except where explicit authority has been granted such as that seen, for example, under the infant formula provisions, Section 412(b)(4)(A)(i), and more recently under the Bioterrorism Act, Section 414(a).

As noted above, BC understands the need for FDA to review and under some circumstances have copies of the cGMP records. In the past we have cooperated with FDA in this regard during our dietary supplement audits and will continue to do so. We also believe the industry as a whole is in agreement with this philosophy. However, mandating access to these records without the appropriate authority from Congress is over-reaching. BC is requesting that FDA clarify the justification for mandating access to these records or alternatively delete proposed Section 111.125(c).

Definition of Sanitize

Proposed Section 111.25(e)(1) would require that companies maintain, clean, and sanitize, as necessary, all equipment, utensils and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements. The current food cGMP definition of "sanitize" under 21 CFR Part 110 requires that contact surfaces be cleaned by a process that is effective in destroying microorganisms of public health significance. The proposal's definition of "sanitize" in Section 111.3 goes beyond the definition as currently found under food cGMP's in that it

[3] Record keeping requirement under the proposal include records pertaining to (1) Calibration of instruments and controls; (2) automatic, mechanical, or electronic equipment calibration, inspection, or checks; (3) production and process controls; (4) quality control; (5) receiving components, dietary supplements, packaging, and labels; (6) master manufacturing and batch production; (7) packaging and label operations; (8) returned dietary ingredients or dietary supplements; and (9) consumer complaints.

requires that cleaned contact surfaces, when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance.

FDA has stated in the proposal that while the manner in which a tolerable level of risk is achieved is not specified, you must validate that control measures are scientifically sound and appropriate to its operations. We interpret this statement as requiring verification that the stated level of reduction is accomplished by the sanitizing procedures employed. BC believes that a yield reduction of 5 logs may be impossible to demonstrate if the pre-sanitization level is at or near the lower detection limit of the test method employed. Thus, verifying the 99.999 level of reduction may be more rigorous that verifying the absence of these microorganisms, that in our opinion, is already required by the current definition of sanitize under the food cGMP's. The only way to verify that the sanitizing process used is effective in "destroying" vegetative cells of microorganisms of public health concern is to verify their absence on the cleaned contact surface. Thus, BC believes that the proposal as written may be more burdensome to verify without providing additional assurance that sanitizing procedures have effectively "destroyed" microorganisms of public health concern.

For the reasons given above, BC believes that the cGMP for food definition of "sanitize" should be retained for the purposes of cGMP for dietary supplements. However, if the agency disagrees with this assessment and believes that parameters must be provided for the level of risk associated with "effectively destroying microorganism of public health concern, we suggest the following alternate language for the definition of sanitize under proposed 21 CFR 1111.3: "Sanitize means to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned contact surfaces that when evaluated for efficacy either, (1) yield a reduction of 5 logs, which is equal to a 99.999 percent reduction or (2) confirm the absence of representative microorganisms of public health significance[4] and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

Temperature and Humidity Control

Proposed Section 111.20(d)(5) that would require the use of equipment to control temperature and humidity in your plant. The example cited by FDA for the need for such equipment was high temperatures in a facility that may stimulate the reproduction of microorganisms and pests that may in turn contaminate components, dietary ingredients, dietary supplements and contact surfaces. BC believes that this requirement is excessive and overly prescriptive with regard to ensuring that dietary ingredients and dietary supplements are not contaminated.

BC believes that while it may be necessary to monitor the temperature and humidity of certain activities relating to the manufacturing, packing and holding of dietary ingredients

[4] The definition of microorganism is broadly defined in proposed Section 111.3 to include species that have public health significance. BC believes that this definition should explicitly state the microorganisms of concern. Suggested alternative language for this definition and other provisions under the proposal are found later in our comments.

and dietary supplements, controlling the temperature and humidity of all operations may not be possible nor necessary if other controls are in place to ensure that the physical condition under which the activities occur do not alter the quality of such substances. For example, bulk supplement blends may be manufactured and stored outdoors where temperature and humidity control are completely impractical. Nonetheless, other controls are in place, such as finished product testing, to confirm that the condition under which the product is manufactured, held or packed does not adversely affect its quality. Thus, if data is available to show that the temperature and humidity of the facility does not alter the quality of the products controlling these parameters becomes excessive. BC is therefore requesting that proposed Section 111.20(d)(5) be revised as follows to allow for the use of alternate methods to ensure that temperature and humidity do not adversely affect the quality of the product: "When necessary use equipment to adequately control temperature and humidity."

Use of Authorized Components

Proposed Section 111.35(d) would require, in part, that components of dietary supplements must be (1) authorized for use as a food additive under Section 409 of the FFDCA; (2) authorized by a prior sanction consistent with 21 CFR 170.3(l); (3) if used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement, or (4) generally recognized as safe (GRAS) for use in a supplement. The proposal further requires that any claim that a substance is GRAS, must be supported by a citation to the agency's regulations or by an explanation, in a company's files, as to why the substance asserted as GRAS, is in fact GRAS. FDA's letter of no objection provided in response to a GRAS notification cannot be used as a basis for asserting compliance to this requirement. The actual GRAS determination must be in the dietary supplement manufacturer's file.

BC does not object in principle to the proposed requirements under Section 111.35(d) as specifically related to GRAS substances. We understand the need to ensure that GRAS substances used in dietary supplements and other foods are indeed GRAS under the manufacturers specific use. However, we do not believe that FDA can mandate by regulation that GRAS determination must be in the dietary supplement manufacturer's files. This action goes beyond the very premise by which, statutorily, a substance can be considered GRAS. In addition, FDA's statement that a letter of no objection provided in response to a GRAS notification cannot be used as the basis for assuring that components used in dietary supplement products are indeed GRAS, puts into question the purpose and utility of the GRAS notification process.

Under the statutory definition of a food additive, a substance can generally be recognized as safe when a group of qualified experts have evaluated the substance using scientific procedures and found it safe under the conditions of intended use. Thus, a substance is GRAS if the experts say it is. While FDA may agree or disagree with the experts, the onus is on the experts and the manufacturers to ensure that a substance is indeed GRAS under the specified conditions of use. Even if FDA disagreed with the determination after inspecting the documents, they could not take any immediate enforceable action. Therefore, requiring the supplement manufacturer to have the complete GRAS determination in the file serves no useful purpose.

Further, FDA's position that letters of no objection cannot be used as the basis for asserting that a substance used in the manufacture of dietary supplement is indeed GRAS completely removes the utility of the GRAS notification process. If a GRAS notification cannot be used for purposes of customer assurance, we believe there would be little incentive to submit GRAS notifications. In the end, FDA's attempt to more tightly control the use of GRAS substances may have the opposite effect, as more and more determinations will be made without the benefit of the notification process.

As mentioned above BC does not object to the need to ensure that GRAS substances used in dietary supplements and other foods are indeed GRAS under the manufacturers specific use. Our objection is to FDA's over-reaching approach in their effort to ensure that manufacturers comply with this requirement. BC believes that manufacturers of dietary supplements should be able to decide on the documentation necessary to ensure that substances used in the manufacture of dietary substances meet the requirements of proposed Section 111.35(d)(4). The documentation could take a variety of forms such as FDA's letter of no objection to a GRAS notification with additional certification by the manufacturer that that the intended use is covered by that notification. The documentation should not be limited to the actual GRAS determination as positioned by FDA in the proposed rule.

Testing of Incoming Components

FDA has proposed under Section 111.35(e) and 111.35 (g) to require certain specifications (i.e. identity, purity, quality, strength and composition) for incoming components, dietary ingredients or dietary supplements and to ensure through testing that the specifications as established are met. BC's understanding of proposed Section 111.35 (g)(1) is that if finished product testing[5] includes testing for the specifications established for the components and the dietary ingredients contained in finished product, then there is no need to test the components or the dietary ingredient for conformance to those specifications upon receipt. If this interpretation is correct, BC believes the proposed provision would provide manufactures little to no relief with regard to the complete testing of incoming components and dietary ingredients. In some cases it may not be possible to test for conformance to incoming specifications once the components or dietary ingredients are formulated into the finished product. Even in cases where it is possible to test for incoming specifications at the finished product stage, BC believes that testing to this extent may not be necessary if alternate methods are utilized to ensure that incoming components are suitable for the intended use.

For example, as an alternative approach BC believes that an appropriate vendor qualification program would alleviate the need for complete testing on every lot of incoming components and dietary ingredients. This approach would require manufacturers to certify that vendors consistently supply product that is suitable for its intended use through a combination of vendor audits and product testing. Once the vendor is qualified and a yearly re-certification program is in place, the manufacturer can then rely on the vendor's certificate of analysis and minimal incoming testing to release the component or ingredient for use. Under a vendor qualification program as described

[5] In this scenario finished product testing is the testing performed on the finished dietary supplement product.

above, manufactures are provided with relief from full incoming testing of components and dietary ingredients without jeopardizing final product quality.

BC notes that even under a more stringent drug cGMP regime, vendor qualification programs for incoming components are permitted. As Congress has instructed FDA to prescribe good manufacturing practice for dietary supplements that are modeled after cGMP for food, it is unreasonable and overly prescriptive for FDA to propose cGMP provisions for dietary supplement components that are even more restrictive than cGMP for drugs. BC is therefore requesting that FDA provide for the use of vendor qualification programs under proposed Section 111.35(g).

Verification (validation)

FDA has not proposed verification (validation) requirements for processes that use automatic, mechanical or electronic equipment. However, FDA has asked for comment on whether such verification should be included in a final rule. BC believes that FDA has relied heavily on inspection and testing requirements to ensure that dietary supplement products meet predetermined specifications and quality characteristics. The purpose of a verification requirement would be to ensure that the processes used consistently produced a product meeting these predetermined specifications and quality characteristics. If the processes used fail to produce a product meeting these predetermined specifications and quality characteristic, the product cannot legally be sold. Thus, while verification imposes additional costs on manufacturers, frequently rejected product, adequate rework procedures and extensive in-process and finished product testing may also be costly.

Given the differences in the types of processes utilized by manufacturers of dietary supplements, BC does not believe that verification of processes that use automatic, mechanical or electronic equipment should be mandated by regulation. BC does believe, however, that manufacturers of dietary supplements, depending on the unique circumstances of a particular manufacturing process, may choose to verify processes using a sound verification system. When such an approach is chosen it may not be necessary to develop and monitor specifications at every step in the manufacturing process where control is necessary to assure the identity, purity, quality, strength and composition claimed on the label as required under proposed Section 111.35. A sound, scientific verification system would involve, in part, identifying critical steps of a process and the parameters around which the critical step consistently produces a product that meets predetermined specifications and quality characteristics. Once this is accomplished the amount of in-process testing needed to ensure that product specifications and quality characteristics are consistently met can often be reduced.

In addition, the use of an appropriate verification system may under certain circumstances allow for lot testing as opposed to batch testing. For example, proposed Section 111.35 (g) requires that each finished batch of dietary ingredients or dietary supplements would need testing before it is released for distribution. The requirement does not appear to allow manufacturers to aggregate or otherwise accumulate multiple batches into a single lot of material without extensive testing of each batch. BC believes that with verification of the process and an appropriate testing scheme a manufacturer could demonstrate that lot testing provides sufficient assurance of quality and lack of adulteration.

As noted above BC does not believe that verification of processes that use automatic, mechanical or electronic equipment in the manufacture of dietary supplements should be mandated by regulation. We believe the public will be adequately protected from adulterated dietary supplement products if the requirements as proposed are met. We also believe, however, manufacturers can use alternatives, such as sound, scientific verifications systems, to minimize the extensive inspection and testing requirements as proposed. We therefore are requesting that FDA address these alternatives in the final rule.

BC notes that the description of verification as found on page 12194 of the proposal is almost identical to the definition of validation as found in CDER's "Guideline on General Principles of Process Validation". We are requesting that FDA confirm that for purposes of the proposal the terms "validation" and "verification" have been used interchangeably.

In addition to the specific areas of concern discussed under the above headings, BC suggests the following changes to several of the provisions in an effort to improve clarity.

Suggested Change Under Proposed Section 111.3

As noted previously, the definition of "microorganisms" is broadly defined in proposed Section 111.3 to include species that have public health significance. BC believes that this definition should explicitly state the microorganisms of concern. As dietary supplement products are generally ingested in solid oral or liquid dosage forms we believe it is appropriate to be consistent with the requirements of the United States Pharmacopeia which requires the absence of salmonella spp, escherichia coli, pseudomonas aeruginosa, and staphylococcus aureus. Therefore, the following change is suggested.

"Microorganisms mean yeasts, molds, bacteria, viruses and other similar microscopic organisms having public health or sanitary concerns. This definition includes, but is not limited to, species that:

(1) Have public health significance (*Salmonella spp, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus)...*"

Suggested Change Under Proposed Section 111.10(b)(8)

Proposed Section 111.10(b)(8) delineates hygienic practices for those who work in operations during which adulteration of the components, dietary ingredients, dietary supplement or contact surface may occur. The proposal specifies that precautions should only be taken in areas where these items are exposed. While BC agrees that the areas where components, dietary ingredients, dietary supplement and contact surfaces are exposed pose the greater risk, we also believe there is a risk of adulteration where these items are held (i.e. stored in containers and not exposed by definition). We also believe that the use of the word "processed" as opposed to "exposed" would cover all areas intended to be covered by the proposals original language and alleviate the need to specify that the requirement applies to areas where contact surfaces are washed. Therefore the following change is suggested.

" (8) Not eating food, chewing gum, drinking beverages and using tobacco products in areas, where components, dietary ingredients, dietary supplements, or any contact surfaces *are held or processed*; and..."

Suggested Change under Proposed Section 111.20(d)(4)

Proposed Section 111.20(d)(4) states the precautions that should be taken for fans and other air-blowing equipment to minimize contamination. BC believes that exhaust and venting equipment can also be a source, under certain circumstances, for microbial contamination. Therefore, the following change is suggested.

" Fans and other air-blowing *or exhaust and venting* equipment located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces..."

Suggested Change under Proposed Section 111.25(a)(4)

Proposed Section 111.25(a)(4) requires that equipment and utensils "have seams that are smoothly bonded or maintained" to minimize contamination. While the phrase "or maintained" provides some leeway for the type of equipment that is used BC believes that provision is overly restrictive and can be improved, without compromising intent, by making the following change.

"Equipment and utensils you use *must be of proper design* and maintained to minimize accumulation of component, dietary ingredient, or dietary supplement particles, dirt, filth, organic material, or any extraneous materials or contaminants to minimize the opportunity for growth of microorganisms..."

* * * *

In summary BC believes that FDA has placed an excessive burden on manufactures of dietary ingredients by exceeding Congress's mandate to prescribe cGMP for dietary supplements. We also believe many of the proposed provisions are similar to or in some cases even more restrictive than drug cGMP which also goes beyond Congress's instruction to FDA to model the requirement after food cGMP. Finally, we have suggested alternate wording for several of the provisions in an effort to improve clarity. We appreciate the opportunity to comment on the proposed regulation and respectfully request that FDA take them into consideration before issuing a final rule.

Sincerely,

Suzanne Matuszewski
Manager
Product Stewardship and Regulatory Affairs