FDA Proposes Regulations on Current Good Manufacturing Practices (cGMPs) in Manufacturing, Packing, or Holding Dietary Supplements and Dietary Ingredients

The Food and Drug Administration (FDA) has now published its long-awaited proposed rule describing the current good manufacturing practices (cGMP) for the manufacture, packaging, or holding of dietary ingredients and dietary supplements. 68 Fed. Reg. 12158 (March 13, 2003). The industry-wide standards would specify requirements for personnel, design and construction of physical plants, equipment and utensils, quality control protocols, recordkeeping, holding and distribution, and handling consumer complaints. The proposal is based in part on dietary supplement cGMP standards developed by various industry groups and trade associations. Although FDA found that these proposals were a useful starting point, the Agency did not believe that any of them were sufficient without additional modification. Interested parties may submit comments on the proposed rule by June 11, 2003.

The nominal purpose of the proposed cGMP regulations is to establish the minimum practices necessary in the dietary supplement industry to protect consumers from adulterated and misbranded dietary supplements due to improper manufacturing, packaging, or holding practices. The rule seeks to address issues associated with the manufacturing, packaging, and holding of dietary ingredients and dietary supplements, such as subpotency, superpotency, contamination with filth, bacteria, microbial organisms or drug ingredients, variation in tablet size or color, mis-filled containers, mislabeling, and use of improper packaging.

Several aspects of the proposal raise potentially troubling issues for the dietary supplement industry, including the record-keeping and access requirements, the need to establish a quality control unit, and, perhaps most significantly, the limitation on the options to document the lawful food-use status of other ingredients in a dietary supplement product. An overview of the proposed cGMP requirements is presented below.

- Relationship to Food GMPs

Enacted in 1994, the Dietary Supplement Health and Education Act (DSHEA), amended the Federal Food, Drug, and Cosmetic Act (FDC Act) to establish a framework for regulating dietary supplements. Among other provisions, the Secretary of Health and Human Services (through delegation to FDA) was given the authority to promulgate regulations establishing cGMPs for dietary supplements. These requirements were to be “modeled after” cGMPs for food and be within the confines of currently available analytical methods.

FDA took pains to describe how the proposed regulations have been “modeled” after the food GMPs, which the Agency describes as a “preliminary pattern” for the dietary supplement cGMPs. However, the proposal goes further than the food GMPs in several instances. In particular, the proposal would require:

- Extensive record-keeping on almost every aspect of operations.
- Calibration of instruments and controls used in the manufacturing or testing of a component, dietary
ingredient, or dietary supplement, as well as documentation of these activities.

- Control and auditing of automatic, mechanical, or electronic equipment as well as records of each review.

- Establishment and use of a quality control unit to oversee the manufacturing, packaging, and holding of dietary ingredients and dietary supplements; such unit would review and assess each operation and would be responsible for material disposition decisions.

- A system of production and process controls, reviewed and approved by the quality control unit, designed to ensure that the dietary ingredient or dietary supplement is manufactured, packaged, and held in a way that prevents adulteration.

- Support and substantiation beyond a “generally recognized as safe” (GRAS) notification letter for the use of substances that are GRAS but not within the definition of “dietary ingredient,” subject to a prior authorization, or authorized as a food or color additive.

- Preparation and documented use of a master manufacturing record with identity specifications, as well as controls and procedures to ensure each batch meets those specifications.

- Preparation of a batch production record for each batch of a dietary ingredient or dietary supplement.

- Testing or examination of each finished batch to determine whether the specifications established in the master manufacturing records are met; if there is no scientifically valid analytical method available for such testing, then a company must test each shipment lot of components, dietary ingredients, or dietary supplements and perform in process testing of the dietary ingredient or dietary supplement to assess conformance with the master manufacturing record.

- Visual examination of containers and supplier invoice, guarantee, or certification for components, dietary ingredients, and dietary supplements, and of containers for packaging and labels received.

- Adequate facilities and control processes for laboratory operations.

- Documented packaging and label operations.

- Collection and proper retention of reserve samples.

- Procedures for handling returned dietary ingredients or dietary supplements and documentation of material review and disposition decisions as well as testing.

- Review, assessment, and possible investigation of consumer complaints; a written record would be required for all consumer complaints related to cGMPs.

The proposed cGMPs do not include a requirement for the maintenance and care of grounds surrounding the physical plant similar to that found in the food cGMPs.
General Provisions (Proposed 21 C.F.R. § 111.1 - .6)

The proposed rule on cGMPs would apply to all firms, both domestic and foreign, that manufacture, package, or hold a dietary ingredient or dietary supplement for sale in the U.S., including those involved in labeling, testing, quality control, packaging, holding, and distribution. 68 Fed. Reg. at 12175. In circumstances where a portion of the operation is contracted to another firm, both the firm performing the operational segment and the contracting firm must ensure compliance with the proposed cGMP regulations for that portion of the operation.

The proposed rule would become effective for large companies one year after publication of the final rule; medium and small companies would have two and three years, respectively, beyond the publication date in which to comply with the cGMPs. 68 Fed. Reg. at 12247. Persons engaged solely in activities concerning the harvest, storage, or distribution of raw agricultural commodities for use in dietary ingredients or dietary supplements by other companies would be excluded from the proposed regulation. In addition, the proposed rule would not include foreign firms that manufacture, package, or hold dietary ingredients or dietary supplements that are imported into the U.S. for further processing but that are ultimately exported from the U.S. 68 Fed. Reg. at 12181.

Personnel (Proposed 21 C.F.R. § 111.10 - .13)

The personnel measures proposed for manufacturing, packing, or holding dietary ingredients and dietary supplements are comparable to the current cGMP regulations for personnel in food facilities. The proposed rule would require that a firm take steps to employ qualified employees and supervisors. 68 Fed. Reg. at 12181. This proposal does not include a general standard as to how many employees are necessary but FDA indicates that general manufacturing practices suggest the need for at least two persons, one to perform the work and a second to review manufacturing procedures.

Each person engaged in manufacturing, packaging, or holding a dietary ingredient or dietary supplement, including consultants who advise on any of these operations, must have the training and experience to perform the duties of the position. 68 Fed. Reg. at 12183. The extent and frequency of the training necessary to ensure employee knowledge about operations remain in the manufacturer’s discretion. Experience is a separate requirement to indicate that an employee must have knowledge gained over time, rather than simply training. In addition to the general employee standards, firms would be required to clearly assign the responsibility for ensuring that all cGMP requirements are met to qualified supervisors.

The proposed cGMPs would also require that any person who might be a source of microbial contamination be excluded from operations and that all personnel use hygienic practices to the extent necessary to protect against contamination, including exclusion from certain production areas or other preventative measures. 68 Fed. Reg. at 12181.

Physical Plant (Proposed 21 C.F.R. § 111.15 - .20)

The rule also proposes to regulate the physical plant to help prevent contamination from buildings and facilities. To comply, FDA proposes that the physical plant be designed and constructed in a manner that will protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding. 68
Fed. Reg. at 12184. Physical plants would be required to be of suitable size, construction, and design to facilitate its maintenance, cleaning, and sanitization. Design and construction requirements include providing separate or defined areas of adequate size to prevent contamination or mix-ups of components, dietary ingredients, and dietary supplements. Other adequate control measures, such as computerized inventory controls or automated systems to separate, would be permitted in lieu of physical isolation.

Additionally, the proposed rule would require that the physical plant be kept in a clean and sanitary condition and in sufficient repair to prevent contamination of components, dietary ingredients, dietary supplements, or contact surfaces. 68 Fed. Reg. at 12184. Sanitation requirements include use of appropriate cleaning compounds, sanitizing agents, and pesticides that are free from contamination by microorganisms of public health significance and are safe and adequate under their conditions of use. Only toxic materials used for specified activities - for use in cleaning, laboratory testing, maintenance or operations of the physical plant or equipment - would be permitted to be held or used in a physical plant where contact surfaces, components, dietary ingredients, or dietary supplements are manufactured or exposed.

- Equipment and Utensils (Proposed 21 C.F.R. § 111.25 - .30)

FDA’s proposed rule would require firms to use equipment and utensils that are of appropriate design, construction, and workmanship for their intended use, as well as provide for adequate cleaning and maintenance of such equipment and utensils. 68 Fed. Reg. at 12189. Equipment and utensils of appropriate design and construction would be those whose use will not result in contamination. Firms would be required to maintain, clean, and sanitize, as necessary, all equipment, utensils, and contact surfaces that are used to manufacture, package, or hold dietary ingredients or dietary supplements.

A company would also be responsible for maintaining and calibrating instruments and controls for accuracy and precision and for ensuring that automatic, mechanical, and electronic equipment work as intended. 68 Fed. Reg. at 12191. Firms would need to establish written protocols for calibrating instruments and controls used in manufacturing or testing and document whether the calibration was performed accordingly. In the absence of a self-prescribed procedure for calibration, FDA has proposed the minimum documentation necessary to ensure adequate calibration was performed.

- Production and Process Control (Proposed 21 C.F.R. § 111.35 - .70)

A portion of the proposed rule includes provisions describing production and process controls for manufacturing, packaging, labeling, and holding operations. FDA proposes to require that firms establish and employ a system of production and process controls in all manufacturing, packaging, and label operations. 68 Fed. Reg. at 12194. This includes using a quality control unit to ensure that operations are performed in a manner that prevents adulteration and that dietary supplements and dietary ingredients meet pre-established specifications for purity, identity, quality, strength, and composition. The quality control unit would also be responsible for making material disposition decisions. 68 Fed. Reg. at 12195.

Under proposed §111.35(d), any substances other than a “dietary ingredient” must meet otherwise-applicable statutory and regulatory requirements for safe and lawful use of such ingredients in food. FDA proposes a
requirement that any substance that will or may become part of, or affect the characteristics of, a dietary ingredient or dietary supplement must be authorized for use as a food additive or color additive, be the subject of a prior sanction, or be GRAS for use in a dietary ingredient or dietary supplement. 68 Fed. Reg. at 12195. Where a company believes a substance to be GRAS, it must either cite an authorizing regulation or develop and document an explanation as the basis for their determination. 68 Fed. Reg. at 12196. In the proposed rule's preamble, FDA noted that the Agency's response to a GRAS Notification would not be an adequate basis for taking a GRAS position for the ingredient. For any claim that a non-dietary ingredient is GRAS, a company must maintain a record of the explanation substantiating that position. The extent of the documentation necessary to support a GRAS position is not clearly described in the proposal. However, it would not be surprising to see dietary ingredient/supplement manufacturers put greater pressure on their ingredient suppliers to provide documentation of the basis for the lawful use of the ingredient.

The proposed rule would require that a company establish and follow a master manufacturing record for each dietary ingredient or dietary supplement manufactured and for each batch size to ensure batch-to-batch consistency. 68 Fed. Reg. at 12197, 12203. Such a master manufacturing record would identify specifications for points in the record where control is necessary to prevent adulteration; controls and procedures would then be established to ensure that each batch meets those specifications. In addition, a batch production record would be required to be kept for each batch of dietary ingredients or dietary supplements manufactured. 68 Fed. Reg. at 12205.

The proposed regulation would also require that a company establish specifications for any point, step, or stage in the manufacturing process where control is necessary to ensure that the dietary supplement contains the identity, purity, quality, strength, and composition claimed on the label. 68 Fed. Reg. at 12196. At a minimum, this would include regulatory specifications for all components, dietary ingredients, and dietary supplements received, and for dietary ingredients and dietary supplements at the in process stage as well as for the finished product.

The proposed rule would require performance testing on each shipment received. 68 Fed. Reg. at 12198. FDA does not consider the use of supplier certification or guarantee in lieu of the testing to be appropriate. The proposed rule would require companies to test the final products for adherence to the pre-set specifications, except where a scientifically valid analytical method does not exist. In this instance, companies would be required to test both incoming shipments of components, dietary ingredients, or dietary supplements and in-process materials in accordance with the master manufacturing record.

In addition, the proposed rule would require specifications for packaging that may come in contact with dietary ingredients and dietary supplements to ensure that it is safe and suitable for its intended use. 68 Fed. Reg. at 12212. Reactive or absorptive packaging would not be permitted.

- Holding and Distributing (Proposed 21 C.F.R. § 111.80 - .90)

The proposed rule would require that dietary ingredients and dietary supplements be held under conditions that protect against contamination and deterioration and that components, dietary ingredients, dietary supplements, packaging, and labels be held under appropriate conditions of temperature, humidity, and light to ensure that their identity, quality, strength, and composition are not affected. This requirement would extend to the holding of components, dietary ingredients, and dietary supplements not only in the physical plant but also at any point in
the distribution chain, including in process materials. However, the scope of the proposed regulation stops short of including retail establishments. In addition, components, dietary ingredients, dietary supplements, packaging, and labels would be required to be held under conditions that will not lead to mix-up, contamination, or deterioration. Likewise, the proposed cGMPs require that reserve samples of dietary supplements be held in a manner that will protect against contamination and deterioration.

- **Consumer Complaints (Proposed 21 C.F.R. § 111.95)**

The proposed regulations for dietary ingredient and dietary supplement cGMPs would require companies to compile, in a written record, each consumer complaint related to good manufacturing practices and review each one to determine whether the consumer complaint involves a possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or cGMP requirements. When there is a reasonable possibility that a relationship may exist between the consumption of a dietary supplement and an adverse event, a firm would be required to investigate that consumer complaint. However, an investigation would not be required if the consumer complaint of an adverse event, illness, or injury is unrelated to whether the product is produced under good manufacturing practices. For example, consumer communications regarding issues such as the price or package size and shape do not indicate a possible health hazard or quality issues and would not be considered consumer complaints under the proposed rule.

- **Records and Record-keeping (Proposed 21 C.F.R. § 111.125)**

The final portion of the proposed regulation indicates that a regulated firm is responsible for maintaining certain records to demonstrate its compliance with cGMPs. The records would be required to be retained for three years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with the records. Moreover, under the proposed rule, the firm must have all required records (or copies) readily available for inspection and copying by FDA at all times during the three year period. The form of the record-keeping would remain up to the company's discretion.

Although records are not required for food cGMPs in general, FDA contends that since records are required in “commodity-driven” food cGMPs, recordkeeping can be required for dietary supplements. It is not clear that the Agency's claims to records access are well-supported. For example, FDA has specific statutory authority to review records in connection with infant formula; such authority was not included in DSHEA. In addition, the Agency's citation to HACCP regulations as support of its records authority is circular since the legal basis for FDA to inspect those records has not been tested. The question of access is likely to be the subject of industry comments on the proposal.

The record-keeping provisions would, if adopted as written, explicitly apply to: calibration records; automatic, mechanical, or electronic equipment records; procedure and process controls; quality control records; records regarding the receipt and review of components, dietary ingredients, dietary supplements, packaging, and labels; master manufacturing records; batch production records; records for laboratory, manufacturing, package and label operations; records regarding returned dietary ingredients and dietary supplements; and consumer complaint records.
• Additional considerations

FDA has not proposed regulations on the following issues but seeks comment as to whether each should be included in the final rule:

• Specific requirements designed to prevent the use of materials derived from certain animals from countries with concerns about bovine spongiform encephalopathy (BSE). 8

• Requirements for the maintenance and care of the grounds bordering a physical plant.

• Specific requirements for dissolution, disintegration, bioavailability, or expiration dating, and related testing.

• Requirements that firms establish and follow written procedures for personnel records; maintenance, cleaning, and sanitization; calibration, inspection, and checking of automatic equipment; receiving and testing components, dietary ingredients, dietary supplements, packaging, and labeling; preparing and modifying master manufacturing records; and manufacturing, laboratory, and holding operations.

• Specific requirements for equipment verification.

For further information about FDA’s regulation of dietary supplements, please contact Frederick A. Stearns at 202-434-4288 or via e-mail at stearns@khlaw.com.

1 P.L. 103-417 (1994).

2 21 C.F.R. Part 110.

3 FDC Act § 402(g)(2).

4 For the purposes of this proposed rule, small firms are defined as those establishments with fewer than 20 employees; medium-sized firms are defined as those establishments with 20 to 499 employees; large firms are those establishments with 500 or more employees.

5 FDC Act § 201(ff). Dietary ingredients include: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any these ingredients.

6 For purposes of the proposed rule, “consumer complaint” is defined as a “communication that contains any allegation - expressing dissatisfaction with the quality of a dietary ingredient or a dietary supplement related to good manufacturing processes.” 68 Fed. Reg. at 12252. The definition specifically excludes any adverse event, illness, or injury related to the safety of a dietary ingredient or dietary supplement independent of its cGMP status.

7 See generally 21 C.F.R. Part 129, Processing and bottling bottled drinking water; 21 C.F.R. Part 120 Hazard

8 See 9 C.F.R. § 94.18.