K&L GATES

Food and Drug Alert

October 2007 www.klgates.com

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Impact of New Dietary Supplement Rule on Current Good Manufacturing Practices (cGMPs)

I. Overview

The Food and Drug Administration (FDA) released its final rule on current Good Manufacturing Practices (cGMPs) for dietary supplements in June of this year, more than 10 years after the Advance Notice of Proposed Rulemaking was issued. 72 Fed. Reg. 34,752, 34,942 (June 25, 2007). For the first time, supplements will be distinguished from other food products and subject to their own distinct set of GMP requirements if sold or offered for sale in the United States (U.S.).

This Alert briefly summarizes the most notable provisions of the cGMP rule, particularly as it compares to the previously proposed rule and the current food cGMP regulation, and also discusses some steps supplement companies can take to begin implementing the requirements. Getting an early start on compliance preparations would be prudent for companies since the new dietary supplement rule imposes some rigorous new requirements that more closely resemble drug cGMPs than food cGMPs.

The rule applies to domestic and foreign companies that manufacture, package, or hold supplements for sale in the U.S. and governs supplement production and process controls, packaging, storage, labeling, consumer complaints, records and recordkeeping, personnel, the design and construction of manufacturing plants, and ingredient testing. The effective date of the rule was August 24, 2007, but there is a three-year phase-in period. Companies with more than 500 employees must comply by June 2008; those with fewer than 500 employees must comply by June 2009; and those with fewer than 20 employees have until June 2010.

A. Background

Dietary supplements are legally classified as "food" and are currently subject to cGMPs for food products (21 C.F.R. Part 110). In 1994, Congress authorized the FDA to create and implement dietary supplement cGMPs "modeled after" food cGMPs. During the process of drafting the new rule for dietary supplements, the agency concluded that the existing food cGMPs were inadequate in many respects, including their coverage of processing procedures and their failure to require the establishment of a quality control unit with appropriate responsibilities. As such, provisions covering these features were added to the document.

The FDA's goal in drafting the final rule was to establish quality, process, and recordkeeping controls to help assure that supplements manufactured or sold in the U.S. meet specifications for identity, purity, strength, and composition and are manufactured under conditions to prevent adulteration. The agency was largely successful in providing a flexible framework for companies, large and small, to implement their own finished product testing procedures and critical in-process test control points. At the same time, the cGMP rule will place additional burdens on finished product manufacturers to establish procedures to ensure that their suppliers provide sufficient assurance as to the ingredients' identity and quality.

B. Summary

Food-like cGMP Requirements

Like the food cGMPs, the dietary supplement cGMPs contain provisions governing facilities, methods, practices, and controls used in product manufacturing, packaging, labeling, and holding that are intended to ensure the safety and quality of finished dietary supplement products. Provisions of the new dietary supplement cGMPs that are similar or identical to the food cGMPs include requirements related to personnel (education, training, and cleanliness); physical plant and grounds (construction, maintenance, waste treatment, and lighting); equipment and utensils (design, maintenance, and cleaning); and product and process control systems (quality controls, raw material inspection and storage, defect action levels, packaging and labeling, storage, and transportation).

Unlike the proposed rule issued in 2003 (68 Fed. Reg. 12,157, March 13, 2003), the final rule only applies to companies that manufacture, package, or hold dietary supplement *products*. It does not apply to manufacturers or suppliers of dietary *ingredients*. The final rule also is not applicable to retailers of dietary supplements and the FDA will use its enforcement discretion with regard to products made by practitioners such as acupuncturists and herbalists who are "adequately trained in their profession" and who use the products on "one-on-one" consultation.

The final rule gives companies more flexibility in determining appropriate finished product testing, no longer requiring that each finished batch of the dietary ingredient or dietary supplement be tested against specifications before release for distribution. Also, companies have the option of either testing a subset of finished batches based on a sound statistical sampling or testing all finished batches of the supplements. And companies have more flexibility in determining employees' qualifications and designing the manufacturing facilities.

Drug-like cGMP Requirements

At the same time, many of the provisions are more drug-like in scope. For example, one of the most significant features of the new rule is the requirement that supplement manufacturers confirm the identity of each dietary ingredient prior to use by testing or examination. Under the new rule, reliance on a certificate of analysis or test data from the supplier is not sufficient to confirm dietary ingredient identity. A companion interim final rule issued by the agency at the same time as the final cGMP rule provides some flexibility to the mandatory 100% ingredient testing requirement by allowing companies to petition for an exemption when there are no validated test methods and other controls are in place to verify the ingredient. 72 Fed. Reg. 34,959, 34,968 (June 25, 2007). However, it is currently unclear how FDA will implement the petition process.

Other provisions similar or identical to the drug cGMPs include the creation of a quality control unit with authority to approve or reject a finished product; laboratory controls; the creation and retention of master product, batch product, and control records; expanded recordkeeping and reporting requirements that include provisions related to document retention, access and inspection; expanded packaging and labeling requirements that include controls governing certain product forms (e.g., tablets, capsules, powder, softgels); product complaint controls; and procedures for dealing with returned products and product salvaging.

II. Notable Provisions

A. Production and Control Systems

Under the final rule, dietary supplement manufacturers are required to implement a system of production and process controls to cover all stages of manufacturing, packaging, labeling and holding of dietary supplements to ensure product quality and that the product is packaged and labeled as specified in the master manufacturing record. The quality control provisions require manufacturers to establish control procedures for all processes; specifications; controls, tests and examinations; and deviations from or modifications to control procedures.

Unlike the food cGMPs, the final rule requires supplement manufacturers to evaluate the identity, purity, strength, and composition of their dietary supplements. Every dietary ingredient used in a dietary supplement will be required to meet "100% identity testing," such that manufacturers will be required to conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient.

In addition to dietary ingredients, manufacturers also will be required to confirm the identity of other components. The new rule allows the option to use a certificate of analysis from a component supplier instead of requiring that manufacturers conduct tests or examinations on the components they receive. However, the manufacturers will need to qualify each supplier by confirming its tests or conducting examinations on a regular basis.

B. Storage

The final rule requires dietary supplement companies to follow written procedures for holding and distributing operations. These procedures must include provisions to assure that components and dietary supplements are held under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and final products are not affected. The final rule also requires that dietary supplement companies store components, supplements, packaging, and labeling under conditions that do not lead to their mix- up, contamination, or deterioration. These provisions closely resemble drug cGMPs.

C. Product Complaints

The final rule requires firms that manufacture, package, label, or hold dietary supplements to establish and follow written procedures for handling product complaints. Under the new cGMPs, firms are required to record and retain all product complaints received.

Also, all product complaints must be reviewed by a "qualified person" of the firm who, when necessary, must investigate a complaint to identify possible production or process control failures and any potential deviations from the cGMPs. Decisions concerning whether or not to investigate must be reviewed and approved by quality control personnel, who are also responsible for reviewing the findings of *all* conducted investigations.

FDA already requires that "serious adverse events" be reported to the agency. See "New Adverse Event Reporting Requirements for OTC Drugs and Dietary Supplements," K&L Gates Client Alert (January 2007). FDA encourages companies to notify the agency of product complaints that are not "serious adverse events," but include reports of illness or injury.

D. Recordkeeping Provisions

Under the final rule, dietary supplement manufacturers must keep written records for either 1 year past the shelf life date, if a shelf life date is used, or 2 years post-distribution of the last batch of dietary supplements associated with those records. Dietary supplement records are required to be kept as original records, true copies, or as electronic records. The final rule also requires dietary supplement manufacturers to keep these records available for inspection by the FDA when requested.

The final rule does not require expiration dating on supplements, but companies that use such dating must have stability data to support the shelf life date.

III. Impact

It is too soon to know the full impact of the final rule on large and small supplement companies. However, one thing is clear, manufacturers will need to begin developing internal standard operating procedures ("SOPs") for implementing the requirements as to their products. Some SOPs to consider are: (1) product specific in-process and finished product testing protocols, (2) written procedures to document process controls, (3) written procedures to document the results of tests and evaluations, (4) written procedures with respect to transportation handling procedures, particularly for ingredients that are vulnerable to excessive heat or cold, and (5) written procedures to assure that ingredients received from third-party suppliers meet certain minimum requirements including a complete and comprehensive certificate of analysis.

One area that will require particular focus is receipt of incoming ingredients from third-party suppliers. Because ingredient suppliers are not subject to the final rule, manufacturers are likely to increase the contractual obligations they place on suppliers to assure consistent quality. Some likely demands will be: (1) increased requests for an FDA guaranty under Section 303(c) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 7.12, (2) increased quality control assurances and documentation to establish that ingredients are accurately represented and are of the expected quality, (3) required pre-qualification audits and routine audits by the finished product manufacturer or third-party auditors, and (4) detailed certificates of analysis that include information such as a description of the tests

or examination methods used, the limits of the tests or examinations, and the actual results of the tests or examinations.

While a false certificate of analysis currently only affords the manufacturer with a breach of contract cause of action and no legal redress under the cGMP rule, it is possible that governmental agencies such as the Federal Trade Commission and state attorney generals may become interested in pursuing action against suppliers that provide false or misleading certificates of analysis to supplement manufacturers. If this occurs, ingredient suppliers could be drawn into compliance with the cGMP rule and have legal liability for assuring the identity and quality of the ingredients they are providing to supplement manufacturers. Additionally, consumers may have a private cause of action under some state consumer fraud statutes.

Finally, with the recent melamine contamination of China-manufactured pet food and other food safety issues arising due to the ever-expanding world marketplace, House Energy and Commerce Committee Chairman John Dingell is publicly questioning the FDA's interim final rule which allows for companies to seek an exemption from the 100% identity testing requirement. Even with the exemption from the 100% identity testing requirement, companies must keep in mind that if the supplement contains non-dietary ingredient binders or excipients, they must assure those ingredients are either generally recognized as safe ("GRAS") or comply with the food additive regulations in addition to complying with the other provisions of the cGMP rule.

If you have any questions about the new supplement requirements or establishing internal SOPs, please contact Suzan Onel (202-778-9134 or suzan.onel@klgates.com), Carol Pratt (503.226.5762 or carol.pratt@klgates.com), Yi-Kang Hu (503.226.5728 or yi-kang.hu@klgates.com), Karl Nobert (202-778-9460 or karl.nobert@klgates.com), or any member of the Food and Drug Practice.

We gratefully acknowledge the assistance of Michelle Bradbury, K&L Gates Summer Associate.