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White Paper:

How 21 CFR Part 111 Helps
Dietary Supplement Companies

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On June 1, 2008, the FDA’s Good Manufacturing Practices (GMP) rule for dietary supplements (21 CFR Part 111) went into effect for companies having more than 500 employees. The staggered phase-in for smaller companies is as follows:

- June 1, 2009 for companies having between 21 and 499 employees
- June 1, 2010 for companies having fewer than 20 employees

Also referred to as “the GMP rule,” the regulation is an effort by the FDA to protect consumers while quelling fears of FDA “over-regulation”—a prospect that alarms not only manufacturers and distributors of dietary supplements, but also consumers.

As this paper shows, however, the FDA’s final Good Manufacturing Practices (GMP) rule will benefit both consumers and manufacturers/distributors of dietary supplements.

Consumer concerns

In the case of consumers, the underlying concern is that too much federal regulation (or the wrong kind) could lead to restricted consumer access and skyrocketing costs, similar to what has occurred in the pharmaceutical industry. This fear is fueled in part by anti-regulatory sentiment encountered in alternative healthcare and chiropractic offices, as well as in health food stores and compounding pharmacies (which tend to be more “alternative”).

Consumers are often referred to websites such as saveoursupplements.org, which voices the following appeal:

If you have ever purchased a bottle of vitamins or used an herbal remedy, you are among the millions of consumers of dietary supplements nationwide. Yet today, your access to safe, effective, and affordable supplements is in jeopardy, and we need your help to protect your health and Save Our Supplements.¹

Despite its hype, the saveoursupplements.org website actually provides consumers with helpful information about bills before Congress which the website views as favorable, or unfavorable, to consumer access “to safe, effective, and affordable” dietary supplements. The website applauds the Dietary Supplement Health and Education Act (DSHEA) signed by Clinton in 1994, which, among other things, gives the FDA the authority to establish “good manufacturing practices” (GMPs).²

Industry response to “proposed GMPs”

Nine years after DSHEA, in March 2003, the FDA published its “proposed good manufacturing practices” (GMPs) for industry review.³

According to an article by the American Botanical Council, many industry groups greeted the publication of the proposed GMPs with a sense of relief, although some industry leaders expressed

concerns that the proposed GMPs represented a drug model, with more expensive, possibly excessive, testing requirements than was intended by Congress in DSHEA.⁴

DSHEA limited the FDA's discretion with respect to cGMPs, by stating that the FDA may not impose standards "for which there is no current and generally available analytical methodology," and that "the cGMPs shall be modeled after cGMP regulations for food, not those for drugs."⁵

FDA response to industry feedback

In response to industry comments in 2003 about the proposed GMPs, the final GMP rule released in June 2007 does not require finished product testing. This would seem to satisfy most dietary supplement manufacturers. In the words of a spokesperson from the Natural Products Association:

We believe [the] FDA was responsive to the many industry comments submitted in response to the proposed FDA GMPs in 2003 objecting to the heavy emphasis on finished product testing, especially the requirements for testing every batch of finished dietary supplements for identity, quality, strength, purity and composition, the understanding being you cannot test quality into the product at the end.⁶

Quality requirements of final GMP rule

The final good manufacturing practices (GMP) rule specifies quality requirements for assuring that dietary supplements are:

- Produced in a quality manner;
- Free of contaminants or impurities; and
- Accurately labeled.

The regulation also requires manufacturers of dietary supplements to maintain records and make them available for inspection by the FDA when requested to do so.⁷

To reassure consumers, the FDA website affirms that the rule "addresses only the quality of the manufacturing processes for dietary supplements and the accurate listing of supplement ingredients. *It does not limit consumers' access to dietary supplements; nor does it address the safety of the dietary supplement's ingredients, or their effects on health, when proper manufacturing techniques are used.*"⁸ [Italics inserted.]

Benefits of final GMP rule

The GMP rule should benefit both consumers and dietary supplement companies by safeguarding consumer access to supplements and by helping to assure quality, thereby preventing potential recalls. In the late 1980s, one such recall (of the dietary supplement L-tryptophan) resulted in a virtual ban on the supplement that lasted for years.⁹

Although the GMP rule will likely result in slightly higher costs, especially for dietary supplement manufacturers who are not *already* following good manufacturing practices, consumer fears of runaway costs (such as those that besiege the pharmaceutical industry) are unwarranted. It is important to keep in mind that the FDA is *only* requiring dietary supplement manufacturers to follow good manufacturing practices, which many companies are already doing. It is not requiring manufacturers of dietary supplements to conduct clinical trials, or to test final product, as it does pharmaceutical companies.

This having been said, it is also important to point out that there are many contributing factors to the high cost of drugs. An often overlooked factor, for example, involves the inefficiencies that exist in the pharmaceutical industry, caused by the industry's reluctance to adopt new technology. (For more information on the inefficiencies in the pharmaceutical industry, see the October 2007 *GXP LifeLine* article, "Adopting Technology in the Life Science Industry: Why is it Taking So Long" at http://www.mastercontrol.com/newsletter/oct07_news.html.)

Global applicability of GMP rule

An important part of the FDA's GMP rule is that it applies to "all domestic and foreign companies that manufacture, package, label or hold dietary supplements, including those involved with testing, quality control, and dietary supplement distribution in the U.S." ¹⁰

This is important because many U.S. companies that sell dietary supplements buy them (either as finished products or as ingredients) from other countries and add their own label. In the L-tryptophan case mentioned above, this is what happened. A lot of U.S. companies bought L-tryptophan manufactured by Showa Denko, a company in Japan, and sold it under their own label. When the problem with the Showa Denko L-tryptophan was discovered, it may not have been immediately clear which U.S. companies were involved in its distribution. Given the seriousness of the situation, this may have resulted in an FDA decision to err on the side of caution by recalling all L-tryptophan supplements.

By holding U.S. companies accountable for assuring that all products that bear their label (*or that they even hold*) are manufactured according to current GMP standards, the FDA final GMP rule may help prevent dietary supplements from being taken off the market (as happened in 1989), due to the negligence of a *single manufacturer* whose product was widely distributed in the U.S.

In the final analysis

The FDA's final GMP rule provides a much needed solution for establishing good manufacturing practices in the dietary supplement industry. It will have little effect on the many reputable dietary supplement companies that are already following good manufacturing practices. The rule will reinforce these practices, and help assure that *all companies* follow good manufacturing practices.

The focus of the final GMP rule is on assuring quality during the manufacturing process, rather than on testing final product. This is more in keeping with the intent of DSHEA according to many

manufacturers of dietary supplements, who rightly maintain that “quality cannot be tested into product.”

By helping to assure quality product, regardless of the location where the product is manufactured, the GMP rule will also protect manufacturers and distributors from potential recalls or dietary supplement “bans,” which hurts the industry as a whole.

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MasterControl Inc. is a global provider of GxP process, quality audit, and document management software solutions for life science companies. MasterControl[™] products are easy to use, easy to deploy, easy to validate, and easy to maintain. They incorporate industry best practices for automating and connecting every stage of the product development cycle, while facilitating regulatory compliance. By combining an integrated platform with a continuum of risk-based software validation products and services, MasterControl drives down the total cost of ownership and enables customers to extend their investment across the enterprise. Hundreds of companies, including 50 percent of the top 20 pharmaceutical enterprises, currently use MasterControl solutions for easier compliance, faster validation, and better process management. For more information about MasterControl, visit www.mastercontrol.com, or call 800-825-9117 (U.S.) or +44 118 9812838 (Europe).



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CONTROL

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MasterControl Inc.

Corporate Headquarters:

MasterControl Inc.

6322 S. 3000 E. Ste. 110

Salt Lake City, UT 84121

United States

Phone: 800.825.9117

Fax: 801.942.7088

www.mastercontrol.com

Asian Headquarters:

MasterControl KK

Aios Akihabara 702

3-2-2 Ueno Taito-ku

Tokyo 110-0005

Japan

Phone: +81 (0) 3 6801 6147

Fax: +81 (0) 3 6801 6148

www.mastercontrol.com

European Headquarters:

MasterControl Global Limited

First Floor North Wing

Matrix House

Basing View

Basingstoke

RG21 4FF

United Kingdom

Phone: +44 (0) 1256 325 949

Fax: +44 (0) 1256 325 289

www.mastercontrolglobal.co.uk

Germany Office

Mendelstrasse 11

48149 Muenster

Germany

Phone: +49 (0) 251 980 2140

Fax: +49 (0) 251 980 2149

www.mastercontrolglobal.de

Email: info@mastercontrol.com