



Strategies for Implementing the New GMPs for Dietary Supplements

By Mukesh Kumar, PhD, RAC

Dietary supplements have been in the news a lot of late, mostly for the wrong reasons. Last October, the US Food and Drug Administration (FDA) reported that in 2010 there were three times as many dietary supplement recalls as over-the-counter (OTC) and prescription drug recalls combined. Products marketed as dietary supplements, but containing pharmaceutical ingredients, were the subject of 80 Class I recalls in the first three quarters of 2010, compared to 50 in 2009 and 10 in 2008. In December 2010, FDA announced¹ that it has issued consumer alerts about hundreds of products marketed as dietary supplements but containing the same active ingredients as FDA-approved drugs, analogs of the active ingredients in FDA-approved drugs or other compounds such as novel synthetic steroids that do not qualify as dietary ingredients. These consumer alerts involve more than 80 products marketed for sexual enhancement, more than 70 marketed for weight loss and more than 80 marketed for bodybuilding. On 15 December 2010, the FDA commissioner wrote² to dietary supplement industry trade associations that the agency intends to increase its efforts to alert consumers about tainted dietary supplements and take enforcement actions against manufacturers, ingredient suppliers and distributors under the *Dietary Supplement Health and Education Act* of 1994 (DSHEA) and 21 CFR 111 containing the current Good Manufacturing Practice (CGMP)³ requirements for dietary supplements. The enforcement actions include FDA inspections, consumer warnings, product recalls, product seizures and criminal investigations, and might not involve a Warning Letter before such actions are initiated.

These increased activities by the agency should not come as a surprise to individuals and companies involved in the manufacture and marketing of dietary supplements. DSHEA gave FDA responsibility for ensuring the quality and truthful marketing of dietary supplements. During the late 1990s and early 2000s, FDA conducted numerous outreach activities to collect public and industry comments about how to regulate dietary supplements. The dietary supplement CGMP regulation was proposed in 2003 and finalized in June 2007. Since 2007, enforcement actions have been on the rise. The dietary supplement industry's trade associations agreed with the FDA commissioner's letter that tainted products can be prevented by following CGMP and assured her they would cooperate fully in FDA's education programs and enforcement activities against parties involved in tainted dietary supplements. This article discusses the key elements of the CGMP regulations for dietary supplements and includes my personal experience regarding common issues and suggestions for compliance through simple, logical and easily implementable steps.

Dietary Supplement CGMP Regulations Borrow Heavily From Drug CGMPs

Processes to ensure consistency of the marketed product consist of logical and well-defined steps based on experience with similar products regarding the most common elements that lead to inconsistency across batches of the same product. Hence, rules to assure consistency in the quality and authenticity of a given product should be independent of the product, be it a dietary supplement or a drug. The simplest way to describe CGMP requirements for dietary supplements under 21 CFR 111 is that they are similar to CGMPs for drugs. Common elements include requirements for standard operating procedures (SOPs), raw material and finished product specifications, quality control (QC), master and batch records, change control and complaint handling. A dietary supplement manufacturer must have proper controls in place to ensure the quality of the dietary supplement and its consistent processing. A manufacturer must qualify its suppliers and implement processes to ensure the integrity of the supply chain. For example, a firm that manufactures a dietary supplement must establish specifications for components (ingredients) used in the manufacture of the supplement. These specifications must include limits on types of contamination that may adulterate or lead to adulteration of the finished batch of the dietary supplement, as required by 21 CFR 111.70(b). The firm must verify compliance with these component specifications, as required by 21 CFR 111.75(a). A firm must maintain documentation that dietary supplements were manufactured in conformance with written procedures (21 CFR 111.375) and that dietary supplement components conform to established product specifications. Also, as appropriate, qualification of a supplier must be documented to assure reliance on a supplier's certificate of analysis (21 CFR 111.95).

In layman's terms, dietary supplement CGMPs could be referred to as drug CGMPs "light." This is evident from a careful review of 21 CFR 111 in comparison to 21 CFR 211 that describes the CGMP requirements for drugs (see Table 1). While there are many similarities in the CGMP requirements for the two classes of products, the requirements for dietary supplements are more flexible. For example, the raw material and finished product specifications are left to the manufacturer to define since there are no universally accepted compendia or standard specifications. Similarly the manufacturer is free to choose any scientific testing methods to characterize its product or raw materials based on its own experience or published reports. The requirement for stability studies does not exist in 21 CFR 111, but the manufacturer is expected to define the product's shelf life based on data similar to that for food products. All records must



Dietary Supplement Manufacturers Should Learn From Drug CGMP Requirements

There is a lot of misunderstanding in the dietary supplement industry regarding implementing the new CGMP requirements. Although the requirements have been in effect for more than three years, many manufacturers are not yet compliant. This is evident from the hundreds of enforcement actions taken by FDA. Compliance issues with CGMP regulations are compounded by the fact that many dietary supplements are derived from natural food and plant sources requiring compliance with Good Agricultural and Collection Practices (GACPs) in addition to CGMP. To add to the problem, since the CGMP regulations are quite recent, there is a lack of experts and training material available to guide and consult.

In contrast, CGMP for drugs is very well established. Therefore, a good strategy for dietary supplement manufacturers is to modify the systems available to the drug manufacturers. Documents and practices such as SOPs, batch records, testing methods, vendor qualification methods, QC, change control and complaint handling can be easily applied to dietary supplement manufacturing. The main limitation with

be retained till at least one year after the expiration date of the product or two years beyond the last date for distribution of the last batch of the dietary supplement associated with those records.

Table 1. Comparison of CGMP Requirements for Drugs With Those for Dietary Supplements

GMP Requirement	Drugs	Dietary Supplements
SOPs	Yes	Yes
Personnel Qualifications and Management	Yes	Yes
Records and Recordkeeping	Yes	Yes
Good Documentation Practices	Yes	Yes
Process Validation	Yes	No (but recommended)
Production and Process Control	Yes	Yes
Change Control	Yes	Yes
Quality Control System	Yes	Yes
Separate QA/QC	Yes	No (but recommended)
Equipment Design, Selection, Calibration, Maintenance, Cleaning, Documentation	Yes	Yes
Contamination Control	Yes	Yes
Environmental Monitoring	Yes	No (but recommended)
Raw material Testing	Yes	Yes*
Controlled flow of Personnel and Materials	Yes	Yes
Aseptic Techniques	Yes	No
Records of In-Process Controls	Yes	Yes
Review and Investigate Product Complaints	Yes	Yes
Final Product QC/Batch Release	Yes	Yes
Internal Audits	Yes	No (highly recommended)
Allowing of Returned Product Salvaging	No	Yes
Complaint Handling	Yes	Yes

*You may choose not to do raw material testing if you qualify the vendor.



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transferring drug manufacturing experience to dietary supplements is the ability to manipulate the requirements to customize them for a given product. Making a drastic change to the manufacturing process could not only increase the financial and logistical burden but also might not be necessary to enhance the quality of the product and available documentation.



As mentioned above, despite the similarities in the two regulations, there is a notable difference in latitude. Unlike drug CGMPs, dietary supplement CGMP requirements leave a lot to the reasonable judgment of the manufacturer. Hence, a dietary supplement manufacturer needs to carefully review the current processes and update only the ones needed for compliance. This would not only ease the burden of compliance but also save money and speed up the process.

Many audits show that dietary supplement manufacturers have CGMP compliance issues similar to those of drug manufacturers. The most common issues in dietary supplement manufacturing audits are failure to test raw materials, inadequate supplier and raw material qualification, deficiency in storage and quarantine of untested material, equipment maintenance and assignment to a given step in manufacturing, improper hygienic and cleaning practices, lack of environmental control for adequate storage and to prevent contamination, inadequate documentation and record keeping and inappropriate QC methods. As is evident, dietary supplement manufacturers can save a lot of pain by using drug CGMP and the experiences of drug companies as a learning tool.

Quick Fixes: Strategies for Implementing CGMP for Dietary Supplements

For manufacturers of dietary supplements, these are anxious days. With a more aggressive enforcement approach by FDA and shrinking timelines, a few tips on how to get started with CGMP

implementation might be very helpful. Below are some proven ways to address common issues.

Create Standard Processes

All processes at the manufacturing facility should be conducted according to written SOPs, which should reflect current practices and be updated when processes change for any reason. All personnel should be trained on the SOPs relevant to their responsibilities. Any deviations from or violations of the SOPs should be documented and appropriate corrective and preventive measures taken to avoid repeat occurrences. Adequate processes such as checklists and forms should be incorporated to ensure and document compliance with SOPs. SOP compliance should be evaluated on a periodic basis.

Use Qualified Personnel and Maintain Adequate Facilities

All personnel involved in the manufacture of dietary supplements must have the education or experience to perform assigned functions, be adequately trained on the SOPs relevant to their responsibilities and be supervised for compliance with SOPs. Facilities and equipment must be designed to meet basic requirements for manufacturing products meeting predefined specifications and be maintained under appropriate hygienic conditions.

Incorporate Robust QC Processes

The most common audit findings concern the lack of acceptable QC processes. The purpose of QC methods and SOPs for testing raw materials and ingredients and recording of test results for each batch are occasionally deficient. To avoid deficiencies, establish and follow procedures for the responsibilities of the QC operation, including written procedures for conducting a material review and making a disposition decision and for approving or rejecting any reprocessing. The testing methods should be appropriate and scientifically valid based upon published literature or past history. Formal method validation is not required but strongly suggested. QC is responsible for manufacturing, packaging, labeling and holder and storage controls. The specifications for all materials have to be in place and the methods used to establish those specifications must be available for audit. The QC process should be led by personnel qualified in the testing methods used.

Define Specifications for Raw Materials and Finished Products

Most product withdrawals have resulted from discrepancies between the label and the actual ingredients (different amounts or additional components) found when tested independently by FDA or other bodies. Typically, the manufacturer failed to clearly specify the composition of the finished product or test the raw material appropriately, leading to adulterated product

downstream. Each raw material and finished product should have clear specifications for acceptance. When a range of an ingredient is used, it should be reasonable and conform to most practical and consistent parameters. These specifications should include an appropriate identification test. Each raw material should be accompanied by a Certificate of Analysis (CoA) that contains a description of the test methods, the limits of the test and the results.

Maintain Detailed Records and Follow Good Documentation Practices

Written records should be maintained and stored for a predefined period. When records are maintained electronically, they should comply with 21 CFR 11, which describes the controls and processes for electronic record maintenance. Documentation should be complete and follow principles of ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate). The second most common audit finding is inadequate master and batch records. Maintain a master record from the overall processes for each product and a batch record that corresponds to the information in the master record for each batch manufactured.

Define Supplier Qualification Parameters and Enforce Vendor Compliance

Suppliers of raw materials, ingredients, reagents and equipment must meet specifications defined by the manufacturer. Manufacturers must conduct supplier audits to be sure that the supplier is maintaining appropriate controls over integrity of the material and accuracy of the CoA. For sources of plant-based products, it is advisable to choose suppliers meeting GACP. As with non-plant raw material, plant raw material should meet pre-defined specifications and measures to prevent contamination.

Establish an Independent Quality Assurance (QA) Department

QA is commonly confused with QC. Unlike QC, which is a part of production activities, QA is a management function. QA is the systematic monitoring and evaluation of the various aspects of a facility and its processes to maximize the probability that minimum standards of quality are being attained. The QA department independently audits all functions, maintains adequate documentation, trains personnel and designs the corrective and preventive measures when deficiencies are identified. The department makes sure everything is done according to the appropriate directions, rules and policies in the company. QA also audits suppliers for qualifications and that they adhere to specifications over time.

CGMP Compliance is Easy, Doable and Inevitable

FDA has been aggressively enforcing the current laws about dietary supplements and

seeking support from other government agencies such as the Federal Trade Commission and the Department of Justice, as needed, to make sure manufacturers in violation of these laws are adequately censured and restricted from US markets. FDA has announced it will take all measures needed to protect consumers from products that could potentially harm them. This could be an opportunity for dietary supplement manufacturers to demonstrate that they are equally committed to good quality, reliable and safe products. Despite all the hype and confusion, there are several resources available for implementing CGMP in an easy, logical and reasonably inexpensive manner. Proactive compliance by supplement manufacturers will lead to better products and less chance of FDA action against the company.

References

1. Tainted Products Marketed as Dietary Supplements. FDA website. <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM236998.pdf>. Accessed 27 January 2011.
2. FDA Commissioner's letter to manufacturers of dietary supplements, 15 December 2010.
3. 21 CFR 111: Good Manufacturing Practices for Dietary Supplements. FDA website. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfr/CFRSearch.cfm?CFRPart=111>. Accessed 24 January 2011.



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