Of all the FDA-regulated industries, dietary supplement manufacturers are most likely to fail quality inspections and receive warning letters from the Agency. This article examines why and tells you how to meet regulatory standards.

As of June 2010, the third and final subgroup—i.e., companies with fewer than 20 full-time employees—was required to comply with current Good Manufacturing Practices (cGMP) for Dietary Supplements (21 CFR Part 111). Since the new regulations went into effect, the number of warning letters issued by the US Food and Drug Administration (FDA) has increased every year. According to data obtained through a Freedom of Information Act request, about 70 percent of the dietary-supplement manufacturers inspected by the FDA fail to meet one or more GMP standards [1].

The root of the problem

There's no reason that regulatory compliance should be any more difficult in the dietary-supplement industry than in other FDA-regulated industries, such as pharmaceuticals, food, and medical devices. So why is compliance so poor? A few possibilities:
Many employees in the industry, even those with years of experience, never had to face a quality audit or an FDA inspection until recently.

Too few supplement manufacturers understand how to respond to a Form 483, which cites objectionable or problematic issues discovered during an FDA inspection. Some manufacturers don't take Form 483 observations as seriously as they should. As a result, they don't try hard enough to comply, which may lead to more serious consequences, including receiving a warning letter and being fined.

Some supplement manufacturers lack the time, equipment, and/or properly trained personnel needed to consistently adhere to best practices. Others lack commitment to the principles of continual improvement, quality, and training. These factors, alone or combined, can lead to a variety of GMP violations. Auditors working for NSF International have found that 483s and warning letters most commonly result from breakdowns in one or more of the following 10 categories.

1. Specifications and identity testing. Failure to conduct identity testing or failure to identify the reference standard used when identity testing is conducted are the most common reasons for warning letters in this category.

Sections 111.75(a)(1)(i) and (a)(1)(ii) of 21 CFR Part 111 state that you must establish specifications for identity testing of each dietary ingredient (unless you have an FDA-approved petition for exemption), and you must verify the identity of all other components (unless you have properly qualified your vendors). In so doing, you may need to justify and document how meeting in-process and component specifications will yield an in-spec product. You must also document that the finished dietary supplements do, in fact, meet specifications.

You must also establish specifications for products you receive to package and/or label. You must have documented approvals from quality control (QC) personnel for every specification and for your control system. You must also have QC staff review and approve supplier qualifications (requirements), component specifications, in-process specifications, and tests or examinations for each product specification.

2. Master manufacturing records. The most common reason for warning letters in this category is failure to prepare and follow a written master manufacturing record (MMR) for each distinct formulation of a supplement. The purpose of an MMR is to ensure that finished products are manufactured uniformly from batch to batch.

With that in mind, you need to establish specifications for all the “points, steps, or stages” of the manufacturing process—including all controls and procedures—and those specifications must be met every time. You must also have specifications for how you conduct sampling, testing, and other examinations. QC personnel must review and approve all MMRs.

3. Batch records. Failure to record complete information about the production and control of each batch of a nutritional supplement is the chief problem in this category. The batch record must reflect that the MMR was followed, with no points, steps, or stages left out.

Each batch record must include the date of each step of production, initials of the person(s) verifying each step, and documentation of the required material review as performed by QC staff. Likewise, QC personnel must document and sign all disposition decisions (i.e., how to best handle rejected or returned materials), listing any reprocessing or repackaging steps taken. Finally, the record must note when the batch and the packaged and labeled finished products are approved (or rejected) for distribution.

4. Procedures and documentation. It is essential to have standard operating procedure (SOP) documentation that is up-to-date and bears the required signatures. These documents are to be used daily or each time a procedure is performed. Your employees should know where they are and be trained to abide by them.

During retention periods, you must have all records (or copies of records) that pertain to the retained products readily available for inspection. You must also allow these records to be copied when the FDA so requests. As has often been said, according to FDA inspectors, “If it's not written down, it didn't happen.”

5. Qualification of vendors. Failure to confirm the results of a supplier’s tests or examinations—relying instead upon the supplier’s certificate of analysis (CoA)—is a formula for trou-
ble. It states in 21 CFR Part 111.75 that you must verify the reliability of a supplier’s CofA by confirming its test results.

Furthermore, you must maintain documentation of how you qualified the supplier and periodically re-confirm that supplier’s CofA. The CofA should spell out which test or examination method(s) were used (noting the limitations of such tests) and include the results. Your QC personnel must review and approve the documentation and affirm the basis for qualification and re-qualification of any supplier.

6. Quality control. Failure to provide either a signed approval or rejection from QC personnel for every stage of your manufacturing, packaging, labeling, and holding operations can earn you a warning letter. QC personnel must also conduct a material review and decide how to proceed when: a specification is not met; there is a batch deviation or unexpected event; an instrument or control fails calibration testing; or a product is returned.

Your procedure should be detailed enough to answer “The Five Ws” (who, what, where, when, and why) and include steps for:
- Evaluating the need for action
- Investigating the root cause in a stepwise process
- Determining possible corrective actions
- Setting a timeframe for the action(s) to be taken
- Evaluating the effectiveness of the action.

7. Investigations. Failure to conduct an investigation when something is found to be out-of-spec is not acceptable. Nor is simply re-testing until the desired result is achieved. You must conduct a full investigation to identify the underlying cause of all non-conformances, deviations, improper calibration, complaints, and returns.

Such anomalies require QC personnel to review and approve all decisions about whether to conduct an investigation and then interpret the findings and determine the appropriate follow-up action(s). If an investigation implicates other batches, you must reevaluate your manufacturing process and determine whether any other batches or products may be affected.

8. Returned goods. You must identify and quarantine all returned goods. These products should be destroyed or properly disposed of unless your QC department approves redistribution or reprocessing. If QC staff approves reprocessing, they must also determine whether the product specifications are met, conduct a material review, make a disposition decision recommendation, and approve or reject the returned product’s release for redistribution.

9. Complaints. Failure to keep thorough, written records of complaints is a violation. These records must include the name and description of the product, its batch, lot, or control number; the date the complaint was received; the name and contact information of the complainant; the nature of the complaint, including how the product was used; the reply to the complainant; the findings from the ensuing investigation; and the documented proof of follow-up actions taken.

10. Cleaning control. Obviously inadequate, unsanitary cleaning procedures are a violation of GMPs, but so too are cleaning procedures or products that might adversely affect your product or its safety. Equipment and utensils must be dismantled down to the smallest parts for maintenance, cleaning, and sanitizing. Seams where parts join must be smoothly bonded or maintained to minimize accumulation of materials or contaminants. Equipment surfaces must be accessible, smooth, and non-porous.

All product contact surfaces must be cleaned and sanitized before use, after any interruption, and as necessary during processing. Cleaning compounds and sanitizing agents must be appropriate for the use you intend, safe under their conditions of use, and stored away from product materials and ingredients. Clean equipment and utensils must be stored in a location and manner that protect them from contamination.

The education solution

Ultimately, the best way to avoid FDA warning letters is to train employees in GMP requirements before problems arise. In fact, GMP regulations clearly state that employees involved in manufacturing, packaging, labeling, and holding of dietary supplements must be trained in their respective roles to maintain compliance with 21 CFR Part 111.

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References