A Healthy Step: Applying GMPs to Dietary Supplements

To address customer concerns and meet regulatory mandates, dietary supplement manufacturers must take a hard look at their facilities and processes.

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Most of the world treats dietary supplements like prescription drugs. In Europe, Latin America, and Asia, dietary supplement manufacturers must prove efficacy and must meet strict standards for quality control and quality assurance. In 2003, FDA issued proposed rules that would hold dietary supplement manufacturers in the United States to a similar standard as their counterparts in Europe and elsewhere. On June 25, 2007, FDA issued the final rule to the industry for implementation.

With the issuance of 21 CFR Parts 111 and 112: Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements, manufacturers can expect to fall under the same scrutiny as their colleagues in the pharmaceutical industry. Compliance with good manufacturing practices (GMPs) is critical for companies that want to take advantage of opportunities in the global marketplace. What's more, some manufacturers already are following GMPs—and using the fact to differentiate themselves in a marketplace where consumer confidence is eroding over safety and quality concerns.

The chief barrier, not surprisingly, is cost. FDA estimates that compliance with the proposed rule will cost the dietary supplement industry as a whole $86 million annually and deliver annual benefits of $218 million in fewer recalls and reduced liability. The American Herbal Products Association (Silver Spring, MD) suggests that the actual benefit may be only $21 million, or even less, and the cost of compliance could be at least $700 million. In reality, it will cost money to comply, and the costs will not be insignificant, particularly for an industry built primarily on extremely low-margin products with low per-unit costs. Going forward, however, it will be the cost of coming to bat. Strategic thinking, prudent capital investments, and creative engineering and procedural improvements will be key to staying in the game.

Dietary supplement manufacturers that follow the GMPs can expect to fall under the same level of scrutiny as drug manufacturers. Photo by Jupiter Images.

CHANGES THROUGHOUT THE PRODUCT LIFE CYCLE

A narrow focus on the manufacturing facility alone would be a mistake. Compliance will require revisiting the entire product life cycle, from development through manufacture and distribution. In Europe, dietary supplement manufacturers must prove that their products are safe and efficacious, just as pharmaceutical manufacturers here and abroad must. Companies must conduct clinical trials and file with regulatory health authorities (RHAs). For manufacturers that have not gone through the process, it can be daunting, and mistakes or missteps can result in costly delays or even denials.

Pharmaceutical industry consultants can help design a clinical trial program that conforms with international regulations, guides the company through the regulatory process, and provides valuable insight into product development issues that could impact on approval.

Decisions made early in the product life cycle will drive decisions about process and facility design, including potential future compliance issues, capacity, and technology requirements.

FDA NOT LIKELY TO REINVENT THE WHEEL

Under the new rules, it appears that FDA will apply concepts that it already uses. For example, any GMP guidelines for dietary supplements are likely to be similar to those already applied to the food and pharmaceutical industries. Another, newer concept is the idea of a science-and risk-based approach to product quality regulation. Issued in 2004, "A Risk-Based Approach for the 21st Century" outlines the agency's philosophy of applying scientific rationale and risk hierarchy when implementing programs and performing inspections. The initiative involves both FDA's review of information submitted in applications as well as inspection of manufacturing facilities for conformance with GMPs. With limited resources, FDA will need to use this approach to determine whom to inspect and how—targeting the highest-risk sites to represent the industry and set the standards for compliance and punishment. Science-based risk management places the burden of proof on manufacturers, increasing the demands in such areas as documentation and quality assurance.

Another concept likely to come into play is hazard analysis and critical control points (HACCP), a management system that currently addresses food safety through analysis and control of biological, chemical, and physical hazards from raw material production, procurement, and handling through manufacturing, distribution, and consumption of the finished product. The seven principles of HACCP are:

1. Conduct a hazard analysis.
2. Determine the critical control points.
3. Establish critical limits.
4. Establish monitoring procedures.
5. Establish corrective actions.
6. Establish verification procedures.
7. Establish record-keeping and documentation procedures.

Resources for Regulatory Information

- Current Good Manufacturing Practice for Finished Pharmaceuticals. 21 CFR Part 211.
- Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Final Rule. 21 CFR Parts 111 and 112.
- Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Human Food. 21 CFR Part 110.
- Current Good Manufacturing Practice in Manufacturing, Packing, or Holding of Drugs; General. 21 CFR Part 210.
- EU Directive on Food Supplements. European Directive 2002/46/EC.
- Guidelines for Vitamin and Mineral Food Supplements from Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Uses.
- Hazard Analysis and Critical Control Point Principles and Application Guidelines from the FDA .
- National Advisory Committee on Microbiological Criteria for Foods.
- Pharmaceutical cGMPs for the 21st Century—A Risk Based Approach: Final Report Fall 2004.

Successful implementation of an HACCP plan requires a firm commitment to the concept by top management. It is also FDA's position that current GMPs are an essential foundation.

FINDING THE STARTING POINT

For most companies, the first order of business will be a gap analysis to assess how and where they might be putting themselves at risk. A thorough analysis should look at facilities, personnel training, process documentation, warehousing, and quality programs; identify those areas that have the most impact; and set priorities. Where does the facility vary from international regulatory nutraceutical statutes or from FDA statutes? What are the shortcomings of its utility systems?

What improvements can be made in flow of personnel, materials, and waste handling? Is the manufacturing technology current or could it be more efficient? The analysis should address engineering issues, such as program and process identification; critical utilities systems, such as heating/ventilation/air conditioning (HVAC) and purified water; energy efficiency; and commissioning and compliance. It should also address environmental health and safety issues and regulations. Rest assured that the findings don't always require a new building. In some cases, the changes may be as simple as increasing the quality staff and ensuring that personnel are wearing the proper protective garb, adjusting the cleaning process, or changing the flow of materials through the building. In others, changes to the facility or equipment may be necessary.

For example, one area of significant concern is cross contamination between products. Determining how far

to go to minimize the risk will depend on a number of factors—chief among them being the nature of the ingredients in question. If an ingredient is a potential allergen, it will require a higher degree of risk management than a product or ingredient that is unlikely to cause an adverse reaction. One company may be able to reach an acceptable level of risk by changing procedures—for example, by ensuring that one team is not running production equipment in two different rooms, or by setting up gown-changing areas in between two production areas. Another company may need to make changes in its HVAC system, which is perhaps the single weakest area in most facilities. Although upgrading or replacing an HVAC system can be a large expense, choosing an energy-efficient design might result in operational savings that can help offset the costs—as well as demonstrate a commitment to the environmental values that many of the company's customers share.

In reality, very few dietary supplement manufacturers are dealing with products that require the level of risk management that pharmaceutical companies provide for potent compounds, and so they are unlikely to require high-containment strategies. But products are at risk any time they are exposed to air—where tablets are made and before they are bottled or packaged. It can pay to look at those facilities and processes and take action to minimize risk, such as reducing the number of steps in the production process or changing the procedure for transferring materials. Adjusting the production schedule to make fewer batches can reduce the number of cleanings and, therefore, lower the potential for contamination. Bear in mind, however, that it will be necessary to document the rationale for these procedures. The regulatory bodies, specifically FDA, need to understand the product and process in order to evaluate any potential risk to the public.

Whether the issue is cross contamination or product consistency, the challenge remains the same: to balance procedural and engineering changes in order to manage risk effectively—and cost effectively. The Achilles' heel of procedurally based risk management is that the program is only as good as the people who implement it. A proven engineering solution is always safer. For example, an automated production process is more repeatable than manual batch mixing. Companies that utilize procedural controls will need to be able to provide proof to the RHAs that the procedural controls are effective. Depending on people to be the control always increases risk, and in some cases it is wise to spend money on "people-proof" solutions. If engineering controls are not financially feasible, additional training, signage, and other means may help reinforce the procedural controls. Risk management always comes at a cost, and each company must decide for itself what level of risk it can afford to take.

Complying with Quality Standards: Points to Consider

A consultant experienced with pharmaceutical current good manufacturing practices (CGMPs) can conduct a thorough gap assessment to identify areas for improvement. Below are a few questions that manufacturers might ask about their facilities. Not all relate specifically to compliance, but all are part of the strategic thinking that should drive the process.

Product Development/Quality Control Lab:

- Does the lab have the instrumentation available to meet more stringent product-testing requirements?
- Does storage for chemical materials, including solvents and other potentially hazardous materials, meet local and national regulations and insurance underwriter recommendations?
- Are service and material access to the laboratory kept separate?
- Are service areas clean and divorced from staff offices, work stations, and support space?
- Are the HVAC, exhaust, fluid, and gas distribution systems energy efficient?
- Does the lab have a system to collect bench-top dust?
- Is the exhaust air discharge system designed to minimize fume and contaminant emissions?

Manufacturing:

- Do the facility and processes meet FDA and international manufacturing guidelines relating to personnel, material containment, building flows, quality assurance, and good engineering practices?
- Do the layout, equipment operation, and safety procedures comply with appropriate building codes, technical statutes such as National Fire Prevention Association (NFPA) codes, insurance underwriter recommendations, etc.?
- Does the facility offer the flexibility to expand capacity or to introduce new drug delivery forms?

Warehousing and Distribution:

- Does the materials management system provide GMP-level storage for materials?
- Is the materials management system as accurate and efficient as possible?
- Does the materials management system allow the flexibility to change form of receipt and shipping should shipping modes or customer preferences change?
- Does the materials management system offer sufficient visibility into all warehouse activities?

EXAMINATION ADDS VALUE

As noted above, it does not necessarily require a new facility to meet the international standards of the newly enacted FDA regulations. This is another area for strategic consideration, based on products produced, quantities, and plans for growth, to name a few factors. In some cases, leasing or purchasing another facility might make sense. In other cases, a renovation is the better choice. Large-scale renovations can be phased to spread out the capital requirements. Outsourcing production is yet another option.

Regardless of whether a company builds a new facility from the ground up or works with an existing site, the exercise of moving toward compliance can have benefits that extend beyond the peace of mind that comes from knowing that an FDA warning letter is unlikely. Greater energy efficiency, as noted above, is one possible outcome. A look at production systems might reveal areas that could benefit from debottlenecking solutions. Perhaps warehousing and distribution activities can be streamlined. Statistical process control systems can enhance product consistency and provide a foundation for continual quality improvement. Automation can reduce the likelihood of errors in production or distribution. Automated systems can also support greater efficiency and may allow manufacturers to allocate human resources more efficiently. Information technology solutions exist that can minimize the paperwork burden required for documentation. In most cases, enhancements required for compliance will increase the product's cost per unit, but finding ways to do things more efficiently with fewer opportunities for error can often help balance those costs.

The potential benefits do not minimize the challenge that dietary supplement manufacturers face. A higher level of regulation will clearly make an impact on most companies in the industry. Some will weather the change successfully and others will not, but it is an inevitability that must be addressed. The number of FDA warning letters issued to the dietary supplement manufacturers since 2000 suggests that the industry is already on the agency's radar. Meeting the challenge successfully requires a strategic plan that achieves compliance and provides an acceptable level of risk management within time and capital constraints. A consultant with experience in pharmaceutical-level GMPs can help guide the integrated project development process and provide creative solutions to attain those goals. The result can be products and processes that comply with national and international regulations, minimize safety concerns, and deliver value-added benefits such as operational cost savings and increased consumer confidence. ❖

Determining how far to go to minimize risk will depend on a number of factors.

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