



# Standards for Supplements

Jill Wechsler

**Concerns about the safety and efficacy of dietary and herbal products are generating manufacturing requirements and analytical standards for ingredients.**

**A**s FDA strives to streamline its regulatory process for bringing new drugs to market (see sidebar, “Manufacturing data key to spurring drug development”), efforts to ensure the quality, safety, and efficacy of dietary supplements and herbal medicines are gaining more attention. FDA is working with the Federal Trade Commission (FTC) to crack down on unsubstantiated health claims made by supplement makers. For example, reports of serious adverse events involving weight-loss supplements containing ephedra have led to product seizures and FDA legal action against manufacturers. Researchers also are investigating the possibility that herbal products containing kava are toxic to the liver. Manufacturers and regulators hope that new good manufacturing practices (GMPs) standards will help ensure the safety and quality of supplements on the market and overcome demands to regulate these products more in the manner that drugs are regulated.

## Push for oversight

The Dietary Supplement Health and Education Act of 1994 (DSHEA) protects dietary-supplement makers from having to prove efficacy or even safety before they are released to the market, as is required for pharmaceutical drugs. Manufacturers must only assure FDA that a product is “reasonably expected to be safe.” This approach shifts the burden to FDA to demonstrate that a product poses a significant or unreasonable risk to consumers before it can take enforcement action. DSHEA permits manufacturers to make structure/function claims for supplements (e.g., “relieves stress” or “supports joint function”) but not health claims (e.g., “reduces risk of cardiovascular dis-

ease”), a fuzzy distinction that has generated fierce legal battles.

However, the proliferation of questionable dietary-product health claims and the growth of the supplement market from \$3.3 billion in 1990 to nearly \$18 billion today is prompting government regulators and enforcement officials to call for stronger oversight. Some members of Congress want to revise DSHEA to stiffen government authority to remove unsafe products from the market and to require supplement manufacturers to file adverse-event reports (AERs) with FDA.

In response, FDA’s Center for Food Safety and Nutrition (CFSAN) is establishing a new AER data system for dietary supplements, food additives, and cosmetics to detect more safety signals from the relatively few AERs filed for these products. FDA commissioner Mark McClellan also has launched a program to clarify what health claims can be made for conventional foods, supplements, and other medical products and what scientific evidence is needed to support such claims. More leeway for permitted health claims, though, will be offset by stepped-up enforcement action against manufacturers that make false or misleading statements.

## Seeking GMPs

All parties agree that supplement regulation would be greatly improved if FDA adopted manufacturing standards for the products. DSHEA authorizes FDA to take this step, but the GMP development process has been excruciatingly slow. Manufacturers judged an initial FDA GMP proposal too similar to standards for drugs. FDA tried to move the process forward by publishing a set of standards proposed by manufacturers in 1997 but then was slow to come up with its own version. A proposed rule that was headed for final publication in late 2000 was diverted by the Bush administration for further review. In October 2002, the Department of Health and Human Services finally sent a revised proposed rule to the Office of Management and Budget for clearance

### Jill Wechsler

is *Pharmaceutical Technology’s* Washington editor, 7715 Rocton Ave., Chevy Chase, MD 20815, tel. 301.656.4634, [jwechsler@advanstar.com](mailto:jwechsler@advanstar.com).

## Manufacturing data key to spurring drug development

FDA commissioner Mark McClellan launched a new initiative on 31 January 2003 to speed up agency review processes and improve the quality of submissions for new drugs and medical products (1). The long-term goal is to accelerate the development of truly innovative medical products by reducing the cost of new-product testing and regulatory compliance.

To meet this goal, FDA seeks to reduce the need for multiple review cycles of market applications for new drugs and biologics and plans to extend the program to medical devices and animal drugs at a later date. More-efficient reviews will be achieved by providing better guidance to manufacturers about what data FDA requires to document product safety, quality, and efficacy; by adopting a quality systems approach to FDA's application review process; and by informing manufacturers early on about deficiencies in applications. The agency seeks to improve the quality of communications between itself and sponsors to increase the quality and completeness of applications when they are first submitted.

FDA has found that delays in application processing often occur because manufacturers fail to demonstrate their ability to make a product

according to current standards of acceptable quality and consistency. More than half of the priority new molecular entities applications filed in 2000 and 2001 took more than the desired six months to gain approval, and a prime cause of delay was problems with chemistry, manufacturing, and controls documentation. Major changes in manufacturing also were the most common reason for delays in approving biologics license applications.

FDA plans to hold workshops to discuss ways to improve clinical study design, a move that may address potential manufacturing or formulation problems that could compromise the consistency of test products. To encourage the development of therapies in highly innovative areas, FDA plans to improve agency guidance to help manufacturers navigate the regulatory process for emerging technologies such as cell and gene therapies, tissue-engineered products, therapeutic vaccines, regenerative medicine, and novel drug delivery systems. FDA emphasizes that manufacturers working with such innovative products must improve the quality of sponsors' product manufacturing and quality assessments.

and announced in January that the proposal was coming "very soon."

Officials at CFSAN's Office of Nutritional Products, Labeling, & Dietary Supplements plan to hold public meetings to encourage broad dialogue about this long-awaited policy, but a final rule remains months, if not years, away. The debate is expected to focus on requirements for validation of manufacturing processes and analytical methods as well as on expiration dating of products versus "use before" recommendations. Small supplement makers protest that strict validation policies are unnecessary and too costly, and they object to the extensive stability testing needed to set expiration dates. Nevertheless, once FDA adopts final GMPs, the agency plans to establish an inspection program to ensure industry compliance.

### Voluntary audits

FDA could decide to modify inspection requirements for manufacturers that participate in voluntary quality-audit programs established by private organizations

and laboratories. The National Nutritional Foods Association (NNFA) has a partnership with NSF International to audit and certify the quality of dietary supplements. NNFA requires its member companies to voluntarily comply with its own GMPs. NNFA's standards call for firms to establish procedures and maintain records of plant maintenance, facility sanitation, equipment design, quality control operations, process controls, personnel training, and distribution procedures. NNFA members who want to certify their GMP compliance may sign up for a third-party audit program, a step taken by approximately 40 companies, with 60 more in the pipeline.

The association also has launched a "true label" program that conducts random tests of the ingredients in certain supplement product categories to see if the product ingredients match what is listed on the product label. Compliance with GMPs, explained NNFA executive director David Seckman at a January 2003 Food and Drug Law Institute conference about

dietary supplements, requires companies to understand, analyze, and control their manufacturing and distribution processes and to demonstrate to third-party auditors that they keep required records and meet set standards.

NSF International's program for certifying that individual supplement products meet quality standards recognized by ANSI requires demonstration of GMP compliance. Manufacturers submit products for testing and undergo an audit of production facilities. NNFA and NSF have agreed to accept each other's GMP certification. NSF also offers GMP registration, which is particularly attractive to contract manufacturers that don't want to certify the quality of specific products.

United States Pharmacopeia (USP) also has established a dietary supplement verification program (DSVP) that is available to all supplement firms. Manufacturers may display the DSVP seal on products that USP tests to confirm that ingredients meet labeling strengths, have acceptable contaminant levels, and meet USP manu-

facturing standards. USP conducts laboratory tests of products to evaluate composition, strength, contaminants, and dissolution; reviews manufacturer quality control documentation, test methods, and stability data; and inspects manufacturer facilities to ensure compliance with GMPs.

USP recently announced that it will award its seal to several products in Pharmavite's Nature Made line and to Kirkland products sold in Costco stores. Products offered by Weider Nutrition International and Inverness Medical Innovations are currently undergoing USP's testing process, and other supplement makers are signing up, according to USP vice-president Srinivasan. He believes that the USP audit program complements FDA compliance efforts and that manufacturers that qualify for the USP seal will meet FDA GMP requirements.

### **Standards needed**

Although GMPs and certification are important for ensuring that manufacturers operate high-quality production systems,

they do not guarantee product purity, consistency, or safety. GMPs will help bring all industry players to a higher level of quality, according to Annette Dickinson, acting president for the Council for Responsible Nutrition (CRN), but she added that GMPs can be oversold as a guarantor of quality. Analytical methods and standards are also needed to ensure product purity and safety. Her organiza-

tion, for example, has issued a voluntary quality monograph for omega-3 fatty acids and is updating a publication about safe intake limit ranges of vitamins and minerals.

FDA, USP, NIH, and others have launched several initiatives to analyze and set quality standards for supplements and botanicals. Following are some of the actions that are now under way:

### **Analyzing ephedra-containing products.**

FDA is conducting a systematic pharmacological analysis of ephedra products that are on the market to determine whether they contain synthetic ephedrine alkaloids and thus would qualify as pharmaceutical drugs and be subject to drug regulations. So far, the agency has found that certain supplements marketed as "natural" actually contain pharmaceutical-grade chemicals, ephedrine hydrochloride, and caffeine anhydrous, which makes them illegal and their manufacturers subject to prosecution.

**Updating USP monographs.** USP is updating and expanding ingredient monographs for botanicals and dietary supplements, building on its original charge in 1820 to set standards for natural medicinal products such as chamomile, valerian, and ginger. USP has published 28 monographs for botanicals and more than 100 for other supplement products that are based on more-sophisticated analytical techniques, and dozens more are in the works. The organization also has issued reference standards for amino acids, botanicals, vitamins and minerals, and other products, and they can be used as global standards to ensure product quality, purity, and potency.

**Providing analytical methods.** NIH's Office of Dietary Supplements (ODS) and FDA have awarded a contract to AOAC International to provide accurate and validated analytical methods for 20 supplements during the next five years. An AOAC dietary supplement task group has drafted a priority list for evaluating ingredients on the basis of product market share, FDA safety concerns, and the availability of test methods. Expert review panels will identify the best analytical methods for validating product quality and identity starting with existing laboratory test methods for substances such as beta-carotene, black cohosh, ginkgo, kava, ginseng, and saw palmetto. The program aims to train laboratory scientists to use accepted analytical methods and will disseminate information about official methods through an on-line electronic compilation of analytical methods. Recommended methods may be included in *USP* monographs and other standards.

**Clarifying safety and health claims.** ODS supports a broad research program to de-

velop more information about safety and health claims regarding certain common supplements (e.g., chromium's effect on diabetes and alternative therapies for treating benign prostate symptoms). One initiative would create a database of research about supplement ingredients. ODS also has established several botanical research centers to identify and characterize botanicals, assess bioavailability and bioactivity, identify active ingredients, and explore mechanisms of action.

**Publishing information.** The American Botanical Council (ABC) is seeking to document the value of herbal preparations by publishing more information about these products. In 1996 it issued a translation of German monographs of more than 300 herbs and combinations. ABC subsequently published a more in-depth guide to 107 herbs that are popularly used in the United States. This year it will issue a clinical guide to 29 commonly used herbal medicines that provides information for practitioners about preparation, dosage, adverse events, and herb-drug interactions.

**Evaluating safety.** A joint committee formed by the Institute of Medicine's Food and Nutrition Board and the National Research Council has established a framework for evaluating the safety of dietary supplement ingredients. The panel recently issued prototype monographs and solicited public comment about six common ingredients: chaparral, shark cartilage, glucosamine, melatonin, saw palmetto, and chromium picolinate. The monographs focus on ingredient safety concerns as opposed to health claims and effects and will help FDA detect unsafe substances in supplements.

### Taking responsibility

Manufacturers generally support public-private initiatives to document product quality and curtail illegal claims. Companies hope that the initiatives will promote consumer confidence in supplements and herbal remedies as well as head off more-stringent government regulation. "Industry needs to step up to the plate and take responsibility for products," commented

CRN's Dickinson. She considers third-party validation programs sponsored by USP and other independent laboratories to be a good way to help companies demonstrate their commitment to quality.

At the same time, ongoing legal and regulatory battles about products such as ephedra have undermined public confidence in supplements overall and have prompted closer scrutiny of supplement marketing by FDA, FTC, and state officials. "It's bad for industry, bad for FDA, and bad for consumers for an issue like this to go on for years," Dickinson commented. Supplements may offer health benefits, but manufacturers must be proactive about compiling evidence of product safety and benefits to retain public confidence.

### Reference

1. FDA, "Improving Innovation in Medical Technology: Beyond 2002," [www.fda.gov/bbs/topics/news/2003/beyond2002/report.html](http://www.fda.gov/bbs/topics/news/2003/beyond2002/report.html) (accessed February 2003). **PT**