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SCIENCE DIRECT
Life Sciences 78 (2006) 2049–2053
Life Sciences
www.elsevier.com/locate/lifescie

Proposed rule: Current good manufacturing practice in manufacturing, packing, or holding dietary ingredients and dietary supplements

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Received 20 September 2005; accepted 7 December 2005

Abstract

The Dietary Supplement Health and Education Act (DSHEA) was enacted in October 1994 to promote the health of Americans by ensuring easier access to safe dietary supplements. Many supplements such as vitamins, minerals, herbs and amino acids have been reported to be helpful in chronic conditions (i.e., heart disease, cancer and osteoporosis). Under DSHEA, dietary supplements can be marketed without prior FDA approval; the burden is on this agency to show that a marketed dietary supplement is unsafe. However, DSHEA retained the FDA's authority to issue regulations that require the manufacture of dietary supplements be in compliance with current good manufacturing practice (cGMP) standards, which are needed to ensure their quality. Several quality-related concerns of marketed dietary supplements that came to light since the passage of DSHEA prompted the FDA in 2003 to propose rules for cGMP for the manufacture, packaging and holding (storage) of dietary supplements. This review will present the highlights of these proposed rules, focusing on the legislative history of DSHEA, rationale for proposing cGMPs along with a general discussion of the specific requirements. Given the voluminous nature of the specific details, the reader is directed to the pertinent FDA publications for details. In this analysis, selected scientific and legal issues are also discussed to promote a better understanding and implications of these rules.

Keywords: Dietary supplements; DSHEA; FDA; CGMPs; Proposed rule for dietary supplements

Introduction

Sen. Orrin Hatch stressed the importance of the need for legislation in the area of dietary supplements. Introducing such legislation on the Senate Floor on April 7, 1993, he said:

> The purpose of this legislation is straightforward: to bring some much needed sanity and order to the regulation of the dietary supplement industry. We need to establish a regulatory structure that will encourage good health through the use of nutritional supplements while, at the same time, protect consumer from unsafe products.

This review will present the highlights of the recent cGMP rule proposed by the FDA in the manufacturing, packaging and holding of dietary supplements (Federal Register, 2003). It will focus on the legislative history of DSHEA, definition of key terms and FDA's rationale for proposing this cGMP rule. It will also include a general discussion of the specific requirements; given the voluminous nature of the specific details, the reader is directed to the pertinent FDA publications cited for details. In this analysis, important scientific and legal issues are also discussed to promote a better understanding and implications of these rules for the industry and practitioners of herbal medicine.

Dietary supplement health and education act (DSHEA)

A dietary supplement, under DSHEA, is defined (Bass and Young, 1996a) as:

> A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary

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doi:10.1016/j.lfs.2005.12.020

intake ; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient in clause (A), (B), (C), (D) or (E).

Historically, the enactment of the Federal Food, Drug and Cosmetic Act (FDCA) in 1938 made reference for the first time to foods "for special dietary use" and "the vitamin, mineral and other dietary properties of such foods" (21 USC § 343(j), 1988, Bass and Young, 1996b). A food is considered misbranded "[i]f it purports to be or is represented for special dietary uses, unless its label bears such information concerning its vitamin, mineral and other dietary properties …[and] fully inform[s] purchasers as to its value for such purposes." (21 U.S.C. 343(j)) FDA's initial concern then was substandard products; later it becomes unsubstantiated claims made of such products.

Senate bill (S. 784), after successfully completing the legislative process of law making, became the Dietary Supplement Health, Education Act (DSHEA) of 1994. This public health law gives Americans more control of their health by providing easier access to dietary supplements. At a hearing on legislative issues related to regulation of dietary supplements, Representative Bill Richardson, House sponsor of the companion bill, said "the safe use of dietary supplements could save this nation billions of dollars in health care costs each year if adequate information could be given to the public on the labels and pamphlets and the public was allowed to make choices" (Bass and Young, 1996c). At the same hearing, FDA Commissioner David Kessler said " [T]he challenge to all participants in the dietary supplement debate–Congress, consumers, industry, FDA, and others–is to strike the right balance between ensuring the safety and proper labeling of all these products while at the same time preserving consumers' freedom of choice". During the legislative debate, publications describing beneficial effects of vitamins and mineral, herbs and amino acids were cited, profusely. (Bass and Young, 1996c).

The passage of DSHEA can be attributed to a combination of the following factors; growing public interest in heath, the scientific evidence that some dietary supplements are beneficial in combating a variety of diseases, strong lobbying efforts by the dietary supplement industry and FDA position on "structure/function" claims that was unacceptable to members of the public, concerned industry, and law makers. The first three will not be discussed because they are generally known; besides, they are too broad to cover in a single article. The last stated reason is discussed because it will help the reader better understand DSHEA and the reasons for proposed cGMP rules.

To understand FDA's position on "structure/function" claims, it is important to know definitions of a "drug" and a "misbranded drug". In pertinent part, a drug is defined as "articles (other than food) intended to affect the structure or any function of the body of man…" (Bass and Young, 1996d), and (b) A drug… is deemed to be misbranded (a) if labeling is false or misleading (21 U.S.C. § 352). In the 1940s, the FDA began using provisions of this Act to declare dietary supplements and other foods to be drugs based on their label or literature claims. This position of the FDA is illustrated by the *Kordel* case. Kordel, the seller of vitamins, minerals and herbs was convicted on 20 counts of "introducing or delivering for introduction into interstate commerce a misbranded drug"; each count carried a US$200 fine (United States v. Kordel, 1947) Along with the product, the manufacturer had also published and sold booklets that claimed the products "are recommended for relieving stomach agonies, general weakness, anemia, premature old age, high blood pressure, liver troubles, failing eyesight, sore feet; maintaining blood energy, muscular activity , sound teeth and gums, healthy skin, hair and eyes, normal functioning of the pituitary and thyroid glands, stomach, intestines, colon, liver and kidneys; and preventing arthritis and stiff joints, excess weight, catarrh, nervous breakdown, sterility and paralysis. These claims were considered "dangerously misleading" by medical experts. Both the appeals court (United States v. Kordel, 1947) and the Supreme Court (Kordel v. United States, 1948) upheld the trial court's verdict.

The most significant change that DSHEA effected was shifting of the "burden of proof" with respect to safety from the manufacturer of a dietary supplement to the FDA. Under DSHEA, a dietary supplement or ingredient can be legally marketed if "it does not present a significant or unreasonable risk of illness or injury" when used as "recommended or suggested in labeling" (Bass and Young, 1996e). As a practical matter, DSHEA allows for marketing of a dietary supplement without prior FDA approval; then if a dietary supplement is dangerous, the FDA has the burden to show that it is not safe. Before DSHEA, the FDA's general strategy to block the marketing of a dietary supplement was to use the provisions of the Food Additives Amendment of 1958 (21 U.S.C. 348 (a)) to show that such a product was adulterated and/or misbranded, which would then make it illegal to market it. Under the food additive provisions, an FDA affidavit charging that a dietary supplement was unsafe, left the manufacturer with two options: (1) it could show that use or intended use of the additive is in compliance with FDA regulations regarding its safe use (if such regulations existed, it would seem unlikely that the FDA would issue the affidavit) or (2) it is generally recognized as safe (GRAS), and hence not a food additive.

The following case (United States of America v. An Article of Food, 1982) illustrates this FDA strategy: The FDA had seized for condemnation lots of Aangamik 15 tablets (also known as Vitamin B-15, Pangamic Acid) marketed by FoodScience Laboratories ("FoodScience"), since they were deemed to be both adulterated and misbranded. The FDA had claimed that (1) the tablets were adulterated since they contained a food additive (*N*,*N*,dimethylglycine hydrochloride, "DMG") which the FDA alleged was unsafe and (2) was misbranded because the label erroneously described the product as "Vitamin B-15", though calcium pangamate is neither a vitamin nor a provitamin, and there was no scientific evidence about its nutritional value or need in humans. Under the law, in pertinent part, a food is adulterated if it contains any "unsafe" additive. An additive was presumed to be unsafe, unless the Secretary of Health and Human Services ("Secretary") exempts

it by "prescrib[ing] conditions under which such additive may be safely used" or had provided for "investigational use by qualified experts". Both parties had stipulated that Aangamik 15 is a food, and the Secretary had not issued any relevant exemptions. The issue then became: Is DMG a "food additive". According the to two-part legal definition (truncated for relevance), of "generally recognized as safe (GRAS)", a food additive:

> [Means] any substance the intended use of which results or may be reasonably expect to result, directly or indirectly, in it becoming a component or otherwise affecting the characteristics of any food, if such substance is not generally recognized among experts qualified by scientific procedures… to be safe under the conditions of its intended use.

The trial court ruled that DMG is a food additive; that ruling was upheld by the appeals court, since it met the "component" requirement (see the first part of the above definition). The second part of the definition requires FoodScience to show that DMG met the GRAS standard. All 5 FDA experts testified that DMG is not generally recognized as safe; while 4 experts for FoodScience testified that DMG was safe at doses used, only one of them testified that it met the GRAS standard. Since DMG met both requirements of a food additive and it was not exempted by the FDA, the tablets were declared to be adulterated food, since they contained an unsafe food additive. Since DMG 15 was ruled to be a food additive, it became the responsibility of FoodScience to show that it was safe; if it was ruled that DMG was not a food additive, it would have been the FDA's burden to show "by a preponderance of evidence that DMG is injurious to health". It is now easy to understand the reasons the industry would be interested in or like to remove dietary supplements from the "reach" of the food additive regulations.

Proposed cGMP rule by the FDA

The proposed cGMP rule, along with background and explanation (about 100 printed pages long), was published in the Federal Register on March 13, 2003 (Federal Register, 2003); as required by law, comments were solicited from potential stakeholders. Final rule is expected in 2005. The Table of Contents is organized under the following sections: (I) Background, (II) General Issues, (III) Description of the Proposed Rule, (IV) Statement Concerning the Use of Plain Language, (V) Paperwork Reduction Act of 1995, (VI) Environmental Impact Considerations, (VII) Analysis of Impacts, (VIII) Federalism, (IX) Request for Comments and (X) References. Of these, the first three sections would be of most interest to scientists because they summarize and discuss background issues such as information on DSHEA, results from an earlier FDA effort to obtain stakeholder input (Advance Notice of Proposed Rule Making, ANPRM, 1997), industry and consumer outreach efforts, the rationale for the proposed rule, including the three key questions the FDA answered before proposing this rule, and the legal authority to propose this rule. These sections will therefore be the focus of this review and analysis.

Legal authority

FDA was granted legal authority under DSHEA to require that dietary supplements be manufactured in compliance with cGMPs. While DSHEA relaxed the regulatory hurdles for marketing of dietary supplements, lawmakers retained FDA's regulatory oversight to protect the public from substandard or dangerous dietary supplements. Specifically, DSHEA states "[t]he Secretary of [HHS] may by regulation prescribe good manufacturing practices for dietary supplements" (U.S.C. 342 (g) (2)). The law also requires that "such regulations shall be modeled after current good manufacturing practice regulations for food". Subsection (g) (2) further states that "[T]he Secretary may *not impose* standards for which there is no current and generally available analytical methodology (emphasis added)." In connection with this last requirement, the FDA could face potential legal challenges from the industry if the proposed rules for detecting viruses are made final (see infra).

Before proposing cGMP regulations for dietary supplements, the FDA considered 3 major issues. The first was whether they were needed. The next issue was the need to recognize the technical feasibility of implementing the proposed standards. The third issue was how the FDA would assist the industry with regulatory compliance. This report will focus on the first two issues because they deal with scientific and legal matters that would be of most interest to scientists.

Need for cGMPs

There has been a growing concern regarding the quality, or the lack of it, of dietary supplements and their impact on public health. In proposing these rules, the FDA listed several specific examples (Federal Register, 2003) of inadequate quality of marketed products (discussed below). The FDA believes, and with good reason, that compliance with the proposed cGMP rules will safeguard public health.

One dietary supplement product in tablet form, which claimed "to gently assist in the systematic cleaning of the body and in the removal of impurities from the intestinal tract" was found to be contaminated with digitalis. This was discovered in 1997 when two women who had ingested tablets of this product suffered from classical symptoms of digitalis-induced cardiac toxicity (Slifman et al., 1998); one of them had a serum digoxin concentration of 3.66 ng/ml, which is about twice the toxic concentration (therapeutic range: 0.9–2.0 ng/ml). A raw material used in the manufacture of these tablets, labeled "plantain" was found to contain *Digitalis lanata.* A nationwide survey showed that about 200 companies may have used this contaminated dietary ingredient, indicating the seriousness of the contamination problem. Identity and purity tests in the proposed rule would have most likely prevented this problem.

A 1998 survey conducted by the American Herbal Products Association (AHPA) showed that many (43) botanicals were contaminated; certain botanicals were contaminated with aflatoxin and mycotoxin. Under the proposed rule, manufacturers would be required to establish specifications for herbals likely to be contaminated and test them for

toxic compounds. A recent article reported that use of certain Ayurvedic herbals has the potential for lead, mercury, and arsenic toxicity (Saper et al., 2004). For example, with one product ("Navaratna Rasa", manufactured by Unjha Ayurvedic Pharmacy), ingesting the recommended dose would expose a child to about 20 000 μg/day of mercury (EPA reference dose: 1 μg /day). The proposed cGMP rule (Federal Register, 2003) has emphasized the need to test imported herbal products for "heavy metals, pesticides and industrial contaminants".

Other issues that were reported are: (a) the use of nonfood-grade chemicals to manufacture dietary supplements (Anon., 1999), (b) unsanitary conditions of manufacture, packaging or storage of dietary supplements, such as pest infestation, equipment and building defects, and leaking pipes. Efforts by FDA have resulted in recalls of dietary supplements contaminated with lead, microorganisms such as Salmonella, Klebsiella pneumonia, "superpotent" products containing vitamins A, D, B6, or selenium. In this connection, FDA cites the recall of certain niacin tablets, because toxicities "such as nausea, vomiting, liver damage and heart attack" have been reported with superpotent niacin at an average level of 452 milligrams of niacin, well above the upper limits of 45 mg daily", established by the Institute of Medicine, National Academy of Sciences. This is interesting since niacin doses as high as 1500 mg/day are used to lower the marker protein lipoprotein (a) in patients with coronary heart disease; it should also be noted that sustained-release dosage forms are used at such high doses to prevent or minimize "flushing" associated with niacin. Recall of subpotent dietary supplements was also initiated by the FDA, such as folic acid; one such product had only about a third (34%) of the labeled amount of folic acid. Since there is considerable evidence that folic acid can reduce the risk of birth defects, such subpotent products pose a danger to public health. In addition, consumers who ingest such products may be under a false sense of security and therefore not seek other relevant assistance. Case laws from the 1930s, show that even then the FDA was battling such products which were either "subpotent (United States v. Lee, 1939) or did not contain the labeled ingredients". The proposed rule would assure that a product contains the labeled amount of the ingredient(s).

The FDA is also concerned about undeclared dietary ingredients such as color additives, lactose and sulfites. The susceptibility of some individuals to lactose is well recognized even among the lay public. The proposed rule will eliminate such problem by requiring dietary supplement manufacturers to maintain master manufacturing records which requires them to list the ingredients present in a product.

High batch to batch variability of the declared ingredients is another reason asserted by the FDA for the need for cGMPs. For example, a product containing ephedrine, pseudo-ephedrine and methylephedrine, the respective batch to batch variabilties were 180, 250 and 1000%, respectively. In one extreme case, one ephedra product contained none of the alkaloid. Similarly, the claimed ingredient was not found in 25% of the gingko biloba products tested, in 20% of saw palmetto products, in 33% of glucosomine, chrondotin and their combination products and in 50% of SAMe (*S*-adenosyl-methionine) products. The proposed rules will, through the establishment of suitable controls, including master manufacturing and batch records, eliminate such variabilities.

Technical feasibility of implementing proposed rules

The FDA stated that, in proposing this rule, it considered only those requirements that were technically feasible. In areas where the science was evolving, the FDA permits "maximum flexibility in meeting the requirement". For example, the proposed rules state that where "tests are available for identity, purity, quality, strength and composition" of certain dietary ingredients or supplements "have not been officially validated, the proposal would permit tests other than those that are officially validated". An officially validated method was defined as "[a] method [that was] validated using an interlaboratory collaborative study by which the proposed method [was] validated by independent testing in separate laboratories under identical conditions" (AOAC, 2005).

The FDA did not propose specific requirements for "dissolution, disintegration, bioavailability, and expiration dating", because the "the scientific study is still evolving". This is reasonable with respect to multi-ingredient products such as herbals where, often all or the major ingredients contained in product are unknown, such requirements would not be feasible. However, for single ingredient dietary supplements like vitamins, the science is readily available to determine such data, and the exclusion of such dietary supplements is rather surprising. Even with a multi-ingredient solid oral dosage form containing some or all unknown ingredients, disintegration data, which can be readily obtained, can be useful (though there is no good correlation between disintegration and bioavailability) in providing preliminary information regarding absorption of the active ingredients. For example, if a product fails to disintegrate, it might be an indication of impaired bioavailability. In this connection, it is important to note only products to be orally ingested come under the definition of dietary supplements; in one case, (United States v Lane-Labs-USA, Inc., 2004), the court ruled that a skin cream, sold by Lane Laboratories for the treatment of skin cancer, was not a dietary supplement because "a dietary supplement must be ingested".

In the proposed rules, FDA has included viruses in the definition of microorganisms, which states, in pertinent part, that "microorganisms means yeasts , bacteria, viruses... having public health or sanitary concern". This inclusion was objected to in one comment, made in response to a similar inclusion in a 1997 FDA announcement (Advance Notice of Proposed Rule Making (ANPRM), 1997) which was a prelude to the 2003 proposed rules; the comment expressed concerns regarding the difficulty in virus detection methods. The FDA has acknowledged this difficulty; however the agency insists on the need for such inclusion because "animal tissues are used in the manufacture of dietary supplements, and the use of virus-containing tissue would adulterate the product". The FDA has as not yet published the final rules. If the requirement of virus free dietary supplements, which safeguards against health risks, is

finalized, it is likely to result in litigation because, under DSHEA, "[the Secretary of HHS] may not impose standards for which there is no current and generally available analytical methodology" (§402 (9)(2), 21 U.S.C. 342; Bass and Young, 1996f).

The proposed rule imposes restrictions on practitioners of herbal medicine who prepare dietary supplements for their patients or clients. Under the proposed rules if "an herbalist practitioner introduces or delivers for introduction into interstate commerce, a dietary supplement or dietary ingredient", the practitioner is considered to be dietary supplement manufacturer. Individual practitioners would have a great difficulty in meeting the cGMP requirements, which are quite, labor intensive. In response to a previous FDA notice (Advance Notice of Proposed Rule Making (ANPRM), 1997), one commentator suggested that such practitioners be exempted from this requirement. The FDA has declined to grant this exemption, insisting that the "risks of adulteration are not eliminated just because the practitioner is an herbalist". This could become a constitutional issue if practitioners of herbal medicine challenge a finalized FDA rule on the basis that it has denied them their livelihood ("property rights", in legal terms) without due process.

Conclusion

In conclusion, this "science-based" rule will require "manufactures to establish and meet specifications for identity, purity, quality, strength and composition of dietary supplements…." Consumers will benefit from knowing that these products do contain the labeled ingredients, and do not contain toxic or undeclared ingredients. While regulations, such as this proposed rule, are meant to protect society, they will also impose an economic burden on those they protect. It is expected that some of the affected parties will disagree with the proposed rule; it may even be challenged in the courts, if finalized against such opposition. Lobbying efforts to reverse the finalized rules can also be expected. Scientists can play a major role by developing cost-effective means to manufacture and test dietary supplements in compliance with proposed cGMPs.

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