

Regulation of homeopathic drug products

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A central recommendation of the most recent report of the Institute of Medicine (IOM) on complementary and alternative medicine (CAM) was that Congress amend the existing statute governing the regulation of dietary supplements, the Dietary Supplement Health and Education Act (DSHEA).¹ The IOM committee that authored the report estimated that over 15 million Americans use herbal products or high-dose vitamins in conjunction with prescription drugs. The safety of these CAM products, therefore, has become a public health imperative.

At present, CAM products that are intended for ingestion—such as herbs and dietary supplements, as opposed to procedures such as acupuncture and massage—are subject to one of three regulatory mechanisms, depending on whether they are classified as drugs, dietary supplements, or homeopathic drugs. The regulatory scheme for conventional drug products based on premarketing clinical trials is widely discussed in public policy debates. The mechanism for dietary supplements, which relies primarily on postmarketing regulation and covers the vast majority of CAM products, is also broadly debated. The process by

Purpose. The regulation of homeopathic drug products is discussed.

Summary. Homeopathy is a system of medicine based on the observation that high doses of pharmacologically active substances cause symptoms when administered to healthy individuals. These same substances, when prepared in very dilute form, may relieve similar symptoms in conditions resulting from different etiologies. Unlike dietary supplements, homeopathic drugs are subject to the Food, Drug, and Cosmetic Act and regulations issued by FDA. Instead of the new-drug-approval process, premarket approval for homeopathic drugs is by way of monograph approval by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS). Monographs are published in the *Homeopathic Pharmacopoeia of the United States*

(*HPUS*). The criteria for inclusion in the *HPUS* require that a homeopathic drug product be determined by HPCUS to be safe and effective and to be prepared according to the specifications of the *HPUS* general pharmacy section. The long history and established nature of homeopathic drug regulation may provide a model for the regulation of dietary supplements.

Conclusion. Homeopathic drugs in the United States are subject to well-defined regulatory processes that more closely resemble those that apply to allopathic medications than to dietary supplements.

Index terms: Alternative medicine; Food and Drug Administration (U.S.); Food, Drug, and Cosmetic Act; Homeopathic Pharmacopoeia; Homeopathy; Regulations; Toxicity
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which homeopathic drugs are regulated is not as familiar to the public, yet it is an important part of the nation's overall drug regulatory scheme. It is the subject of this article.

Homeopathic drugs

The sale of prescription drugs and dietary supplements is a multibillion dollar business in the United States. While sales of homeopathic drug products are at least an order of magnitude smaller, they are among the top 10 best-selling nonprescription

drugs in the specialty analgesics, oral analgesics for children, and cough-cold-flu categories in the United States out of several hundred products currently tracked.²

Industry estimates suggest sales of homeopathic drugs in the United States in 2003 of between \$300 million and \$450 million, with a compound average growth rate of approximately 8% per year.³ Recent data from the National Health Information Survey indicate that 74.6% of Americans have used CAM as the

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Centers for Disease Control and Prevention (CDC) defines it, while 3.6% of Americans have used homeopathy.⁴ This level of use is roughly double that reported in 1990 by Eisenberg and colleagues,⁵ who may have underestimated the extent of use. Indeed, simple calculation of per capita consumption of \$450 million in retail sales by 3.6% of the population yields an annual consumption level of approximately \$60 per person, a relatively high value considering that average retail prices of homeopathic drugs range from \$5 to \$9 per retail unit.

Homeopathy is a system of medicine that dates back more than 200 years. Its use is based on the observation that high doses of pharmacologically active substances cause symptoms when administered to healthy individuals. Those same substances, when prepared in very dilute form, may relieve similar symptoms in conditions resulting from different etiologies.⁶ The clinical use of certain drugs according to this “like cures like” observation is called the principle of similars and forms the theoretical basis for homeopathy. Vaccines and some conventional medications, such as nitroglycerin for angina, stimulants for attention-deficit hyperactivity disorder, and digitalis for congestive heart failure, have been compared in effect to homeopathy.⁷ Since 1938, homeopathic medicines have been classified as drugs within the meaning of the federal Food, Drug, and Cosmetic Act (FDCA).⁸ Official homeopathic drugs are those that have monographs, which are official listings of drug data, in the *Homeopathic Pharmacopoeia of the United States (HPUS)*. The *HPUS* is prepared by a nongovernmental organization, the Homeopathic Pharmacopoeia Convention of the United States (HPCUS), which is composed of scientists and clinicians trained in the medical specialty of homeopathic medicine.^{9,10} Since most homeopathic drugs are sold on a nonprescription

basis, very few are subject to reimbursement by insurance.

Homeopathy’s regulatory history in the United States

Homeopathy’s introduction into the United States is credited to an American of Danish descent who was trained in Copenhagen, Hans Burch Gram, in 1826.¹¹ By 1871, sectarians—practitioners who were not members of the American Medical Association, including homeopaths—represented at least 13% of practitioners in the United States. By 1880, homeopaths operated 14 medical schools, compared with the 76 operated by conventional physicians.¹² However, by the middle of the 20th century, the professional practice of homeopathy was all but over.¹³ The last pure homeopathic medical college closed in 1920, although Hahnemann Medical College in Philadelphia taught homeopathic electives until midcentury. Nevertheless, the influence of the homeopaths was not completely gone. In 1938, Senator Royal Copeland of New York, a physician trained in homeopathy and a principal author of the FDCA, included within the law’s definition of “drugs” articles monographed in the *HPUS*.⁸ Whether Congress’s acceptance of this definition was a personal concession to Copeland or an attempt by reformers to regulate homeopathic drugs more closely is not clear.^{14,15} The effect was to include homeopathic drugs as a formal component of food and drug law in the United States.

Distinctions among allopathic drugs, homeopathic drugs, and dietary supplements

Before discussing the regulatory context of homeopathic drugs, it is important to distinguish between their status and those of allopathic drugs and of dietary supplements in terms of clinical use and regulation. From the perspective of clinical use, allopathic drugs are used to treat

symptoms, to provide prophylaxis, and to induce structural or biochemical changes in a biological system.

By contrast, homeopathic medicines are used principally for the treatment of symptoms, since, in general, the body must first exhibit symptoms before the correct homeopathic drug may be chosen. Homeopathic medicines are used rarely for prophylaxis, although there are some case reports showing the successful use of homeopathic drugs in epidemic disease.^{16,17}

Dietary supplements include an array of substances, including vitamins, enzymes, herbs, and functional foods.¹⁸ Thus, clinical use of dietary supplements is highly variable. In addition to approved health claims and statements regarding product content and nutrient deficiencies, assertions made by manufacturers are limited to those saying that their products cause the body to maintain “healthy function.”¹⁸ In practice, however, dietary supplement manufacturers routinely make claims that could be interpreted by the public as relating to the structure or function of physiological systems or to the relief of symptoms. For example, claims have been made that dietary supplements help the body maintain natural sleep. The allopathic drug claims for “sleep aids” is effectively the same. Consequently, from a clinical perspective, dietary supplements and allopathic drugs share the goals of prophylaxis and biochemical change, while homeopathic and allopathic drugs share the goal of symptom relief.

The regulatory differences among allopathic drugs, homeopathic drugs, and dietary supplements are no less complicated. Table 1 compares the regulation of the three categories of medications. For ease of discussion, it is helpful to contrast controlling law according to whether it addresses premarket approval, postmarket regulation (manufacturing, marketing, and sales), advertis-

■ **PRIMER Homeopathic drug products**

ing regulation, or reimbursement status for the three types of products.

Allopathic drugs are governed by the federal FDCA and related regulations, published in Title 21 of the Code of Federal Regulations (21 C.F.R.). Premarketing approval is administered by the Food and Drug Administration (FDA) through the new-drug-application process for new drugs, while certain nonprescription drugs that are available for purchase directly by consumers on a nonprescription basis are subject to a separate nonprescription drug-review process. Postmarketing regulation is principally specified in 21 C.F.R. and includes current good manufacturing practices (GMPs) and reporting of adverse drug events. Current GMPs specify the methods and conditions under which drugs must be produced, including validation of equipment and processes and training of staff. FDA regulates drug claims that are included in labeling. Nonprescription drugs are limited to making claims for self-limiting conditions that do not require medical diagnosis or monitoring.⁸ Advertising for prescription allopathic drugs is regulated by FDA, while advertising for nonprescription allopathic drugs is regulated by the Federal Trade Commission (FTC). Reim-

bursement patterns for allopathic drugs vary, but the general rule is that prescription drugs are reimbursed by most private health insurance plans and may be deducted as a medical expense for federal tax purposes, whereas nonprescription drugs are generally not reimbursable but are subject to coverage under qualifying tax-advantaged flexible spending plans.¹⁹

Dietary supplements are regulated under the DSHEA, which was enacted as an amendment to the FDCA. As a practical matter, no premarket approval has applied to supplements currently on the market, since no new chemical entities have been approved since the passage of the DSHEA. All products marketed since the inception of the DSHEA are either single supplements or combinations of products that existed at the time of the DSHEA's implementation. Claims for the products must be reported to FDA prior to marketing,²⁰ and products may be freely sold unless and until the agency objects. Until recently, there was little federal oversight of the manufacturing of dietary supplements. Supplements have become subject to recently promulgated GMP standards of their own²¹; however, some critics point out that GMPs for dietary supple-

ments are less rigorous than those of their drug counterparts.

Manufacturers of dietary supplements may not claim that their products act like drugs. Claims regarding effects on physiological structures and functions are permissible if they do not fall into one of the categories of drug claims outlined by FDA. Among those categories are products claiming to have an effect on a specific disease or class of diseases or on one or more signs or symptoms that are characteristic of a specific disease. Proscribed are implicit disease claims through the name of the product, a statement about the formulation of the product, a claim that the product contains an ingredient that has been regulated by FDA as a drug and is well known to consumers for its use in preventing or treating a disease, or citation of a publication or reference. Also prohibited are claims that a supplement belongs to a class of products intended to diagnose, mitigate, treat, cure, or prevent a disease or that is a substitute for a product that is a recognized therapy for a disease.²² However, even with the great specificity of regulation recently developed by FDA, as previously noted, the line between a drug claim and a dietary supplement claim can be difficult to draw, and advertising of di-

Table 1.

Regulation of Allopathic Drugs, Homeopathic Drugs, and Dietary Supplements^a

| Medication Type | Regulatory Control | | | | | |
|---------------------|----------------------|-----------------------------|---------------------|--|---|----------------------------------|
| | Enabling Legislation | Premarket Approval | GMPs | Labeling | Advertising | Indication on Labeling |
| Allopathic drugs | FDCA | NDA (21 C.F.R. 300 et seq.) | 21 C.F.R. 210 & 211 | 21 C.F.R. 201 | Prescription: FDA Nonprescription: FTC | Required |
| Dietary supplements | DSHEA | None | Proposed | DSHEA | FTC | "Structure-function" claims only |
| Homeopathic drugs | FDCA | HPCUS monograph | 21 C.F.R. 210 & 211 | 21 C.F.R. 201, FDA Compliance Policy Guide 400.400 | Prescription: FDA Nonprescription; FTC | Required |

^aGMPs = good manufacturing practices, FDCA = Food, Drug, and Cosmetic Act of 1938, NDA = new-drug-application process, 21 C.F.R. = Title 21 of the Code of Federal Regulations, FDA = Food and Drug Administration, FTC = Federal Trade Commission, DSHEA = Dietary Supplement Health and Education Act of 1994, HPCUS = Homeopathic Pharmacopoeia Convention of the United States.

etary supplements is regulated solely by FTC. This practice is a result of an agreement between FDA and FTC in 1971 under which FDA took responsibility for the enforcement of regulations concerning prescription drug advertising, leaving FTC with the responsibility for nonprescription articles, including dietary supplements and nonprescription drugs.²³

By contrast, homeopathic drugs are subject to the FDCA and regulations issued by FDA. Instead of the new-drug-approval process, premarket approval for homeopathic drugs is by way of monograph approval by HPCUS.⁸ While homeopathic drugs are also subject to the FDA's nonprescription drug review, FDA has not yet used this authority. However, manufacturing, labeling, marketing, and sales of homeopathic drugs are subject to FDA compliance rules. These rules, with the exception of provisions for expiration dating, tablet imprinting, and finished product testing, are functionally identical to the rules for their allopathic counterparts. GMP standards for homeopathic and allopathic drugs are the same. Advertising oversight and reimbursement for homeopathic and allopathic drugs are also identical.

The *HPUS*

The principal distinction between homeopathic and allopathic drug regulation is in the manner of premarket approval. The *HPUS* has been in continuous publication in one form or another since 1841. Officially recognized in the FDCA, the *HPUS* was published by the American Institute of Homeopathy, a physicians' organization, until 1980, when HPCUS was formed as a separate legal entity.⁹ HPCUS is a standard-setting organization that focuses on the regulatory approval of official homeopathic drug products and the development and publication of general pharmacy practices and standards. At present, 1286 official homeopathic drug products are recognized in the

HPUS, a publication in excess of 1600 pages.

Approval standards of HPCUS

The criteria for eligibility for inclusion in the *HPUS* require that a homeopathic drug product be determined by HPCUS to be safe and effective and to be prepared according to the specifications of the *HPUS* general pharmacy section. The clinical benefits of the new drug must be established in one of the following ways: through clinical verification acceptable to HPCUS, after which there is a period of clinical verification; through published documentation that the substance was in use prior to 1962; through use established by at least two adequately controlled double-blind clinical studies using the drug as the single intervention; or through use established by data gathered from clinical experience encompassing the symptom picture before and after treatment, including subjective and any available objective symptoms.¹⁰

The criterion of clinical use prior to 1962 was used to grandfather many drugs during the 1970s and 1980s into acceptance. This criterion is now rarely, if ever, used, and HPCUS is rereviewing many monographs accepted under this approach. HPCUS reports that the criterion of clinical experience has never been used. Consequently, only the criteria of homeopathic drug "proving" and establishment by two adequate clinical studies are currently in actual use (Baker C, personal communication, 2004 Nov).

Unique to homeopathy, the notion of homeopathic drug proving has its roots directly in the principle of similars. The original homeopathic technique was to administer a dose of a pharmacologically active substance to a healthy volunteer and observe the symptoms that developed. A homeopathic dose of the substance was then administered to an individual with similar symptoms of differ-

ent etiology to determine if the symptoms improved. Modern provings are very similar to this technique. Although methodologies vary, typically a sample population is administered placebo for a pretrial run-in period, followed by a study period of exposure to an infratoxic level of the test substance. Self-reported symptoms are entered into a subject's diary for the entire period, and subjects are followed by a supervisor, who is typically a nurse practitioner. At the conclusion of the active period, symptoms are aggregated and analyzed using both qualitative and quantitative methods. While data captured in this manner are subject to validity errors associated with self-reporting, proper controls can mitigate this limitation. After analysis and acceptance by HPCUS, the data are subject to clinical verification, which involves clinical use of the drug to mitigate symptoms while capturing outcomes data using conventional case-series methods. Overall, adequately designed and well-controlled clinical trials have become the norm for homeopathic medicine as they are for most allopathic medicines.

HPCUS approval process

The process by which judgments are made concerning monographs begins with the submission of a monograph to the HPCUS monograph editor. After review for completeness and formatting, the monograph file is forwarded to the monograph review committee (MRC) for a first review. The MRC is composed primarily of scientists and pharmacists and focuses on the technical aspects of monographs, including substance characterization, quality analysis and controls, assay techniques, and reference reagents, as well as the technical aspects of drug production. After review, the MRC may return the submission to the sponsor for more data or clarification, reject the monograph, or accept the monograph and

recommend publication for a 90-day comment period in journals related to the professional practice of homeopathic medicine.

After publication for comment, the monograph and comments are presented to the pharmacopeia revision committee (PRC) for a second review. The PRC consists primarily of clinicians and concerns itself with the proving or clinical trials data and with a second review of technical information. Both the MRC and the PRC review related toxicology and safety data and make recommendations for the dosages at which the drug may be marketed on a nonprescription or prescription-only basis. About 5% of homeopathic drugs sold in the United States are available by prescription only. Like the MRC, the PRC may request more data on a drug, reject it, or accept it. If a monograph is accepted and differences exist between the MRC's and PRC's opinions, a joint MRC-PRC meeting may be called to resolve them. After preliminary approval by the MRC and the PRC, the monograph, along with recommendations, is forwarded to the HPCUS board of directors, which makes final decisions. If the board accepts the monograph, the sponsor is so advised and clinical outcomes data are requested. HPCUS collaborates with the monograph sponsor to determine the sample size for these data based on standard criteria of effect size, clinical indications for use, and potential toxicity or adverse effects. Once these data are collected and forwarded to HPCUS, the combined MRC and PRC committees review the clinical outcomes data. If acceptable, the monograph is granted final approval for inclusion in *HPUS*, and the drug becomes an official approved drug within the meaning of the FDCA.

The *HPUS* monograph process is substantially different from the new-drug-approval process of clinical trials that start with early dose-response studies that are followed by

larger clinical investigations. The difference reflects the clinical history of homeopathic drugs and the necessity for data-collection techniques that are specific to the therapy. While randomized controlled trials are useful in determining the efficacy of homeopathic drugs, data collection from provings are much more useful in developing a more complete symptom picture that offers insight into clinical effectiveness—not unlike the use of qualitative data or clinical impressions to augment data collected in a randomized controlled trial. The HPCUS monograph process, which has evolved over the past 150 years, produces only a few new homeopathic drugs every decade but carefully reviews those new drugs for safety based on clinical evidence.

Implications for dietary supplements

The long history and established nature of homeopathic drug regulation may provide a model for the regulation of dietary supplements. Instead of relying on a mostly post-market mechanism, supplements could be subjected to a scheme that is similar to the homeopathic mechanism, including an official monograph followed by GMPs and strict regulatory follow-up. This approach would establish a clear pharmacopeia of official dietary supplements, along with standards for identity, manufacture, and quality control and clear guidelines for clinical use—without the need for a complex process of formal premarket clinical trials. Such a step may not address all concerns but would balance the concerns of manufacturers and safety advocates. In this regard, homeopathic drug regulation is a model that deserves wider public recognition and understanding.

Conclusion

Homeopathic drugs in the United States are subject to well-defined regulatory processes that more closely

resemble those that apply to allopathic medications than to dietary supplements.

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