

The Regulation of Homeopathic Drugs as Complementary and Alternative Medicine Products: The Role of the Homeopathic Pharmacopoeia of the United States

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Abstract: FDA classifications and regulation of allopathic drugs, homeopathic drugs and dietary supplements are contrasted. The role of the HPCUS in regulation of homeopathic medicines is described, and the HPCUS drug approval process is detailed.

Keywords: allopathic drug, FDA classification and regulation; homeopathic drug, FDA classification and regulation; dietary supplements, FDA classification and regulation; HPCUS, role of in homeopathic drug regulation and approval.

In its most recent guidance to industry,⁽¹⁾ The United States Food and Drug Administration (FDA) made note of existing confusion related to the regulation of products associated with Complementary and Alternative Medicine (CAM). At present, CAM products that are intended for ingestion are subject to three specific regulatory schema. These products can be classified as allopathic drugs, dietary supplements or homeopathic drugs. These schema have a variety of points of difference, including pre-market approval of the substance, label claims, Good Manufacturing Practices (GMPs) and rules for label claims.

Allopathic Drugs

The regulation of conventional drug products is well-known and understood. Drugs may be of two types - prescription and non-prescription (OTC), distinguished principally by the relationship of the toxic and therapeutic dose range of the drug as well as label claims. Prescription drugs are subject to approval of a New Drug Application (NDA), which utilizes data from clinical trials to establish the safety and efficacy of the drug. OTC allopathic drugs may be sold pursuant to an NDA or according to an OTC monograph that indicates the dose range and indications that are approved by FDA. Good manufacturing practices and labeling guidelines are effectively identical to those of homeopathic

drugs and will be discussed below.

Homeopathic Drugs

Homeopathic drug products are among the top ten best-selling over the counter drugs in specialty analgesics, oral analgesics for children, and cough/cold/flu categories in the United States. Industry estimates⁽²⁾ suggest sales of homeopathic drugs in the United States in 2006 between \$500 million and \$600 million annually, with a compound average growth rate of approximately 8% per year. Recent data from the National Health Information Survey (NHIS)⁽³⁾ suggest that 74.6% of Americans have used Complementary and Alternative Medicine (CAM) as the CDC defines it, while 3.6% of Americans have used homeopathy. This level of use is roughly double that reported by Eisenberg and colleagues in 1990⁽⁴⁾ and is criticized by some in the industry as an under-reporting of the actual use of homeopathic medicines compared to OTC sales. Indeed, simple calculation of per capita consumption of \$500 million in retail sales by 3.6% of the population yields an annual consumption level of approximately \$47 per person, a relatively high value considering average retail prices of homeopathic drugs in the range of \$5.00 to \$9.00 per retail unit.

Since 1938, homeopathic medicines have been classified as drugs within the meaning of the Federal Food and Drug Act (FDCA).⁽⁵⁾ Official homeopathic drugs are those that have monographs in the

Homeopathic Pharmacopoeia of the United States (HPUS). The HPUS is prepared by a non-governmental organization, the Homeopathic Pharmacopoeia Convention for the United States (HPCUS) which is composed of scientists and clinicians trained in the medical specialty of homeopathic medicine. (6,7) Since most homeopathic drugs are over the counter, very few are subject to reimbursement.

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. (8) By 1871, sectarians, including homeopaths, represented 13% of practitioners in the United States, a figure that Paul Starr feels under-represents their numbers; by 1880, homeopaths operated 14 medical schools compared to the 76 operated by the regulars. (9) By the middle of twentieth century, the professional practice of homeopathy was all but over. (10) The last pure homeopathic medical college closed in 1920, although Hahnemann Medical College in Philadelphia taught homeopathic electives until mid-century. (11) But the influence of the homeopaths was not completely gone. In 1938, Senator Royal Copeland, a physician trained in homeopathy, was the principle author of the federal Food Drug and Cosmetic Act (FDCA). Copeland included in the definition of a drug articles monographed in the Homeopathic Pharmacopoeia of the United States (HPUS). (5) Whether this inclusion was a personal concession to Copeland or an attempt by reformers to regulate homeopathic drugs more closely is a question that is still open to debate. (12,13) So whether an accidental artifact of history or a specific attempt at regulation, homeopathic drugs were made an essential part of food and drug law in the United States.

Allopathic Drugs, Homeopathic Drugs and Dietary Supplements

There is considerable confusion among providers and consumers concerning the differences between allopathic drugs, homeopathic drugs and dietary supplements, particularly herbal products. Distinctions fall into two general domains - clinical use and regulation.

From the perspective of clinical use, allopathic drugs are used for symptom treatment, prophylaxis, and to induce structural or biochemical changes in a biological system. By contrast, treatment with homeopathic medicines is principally used for presenting symptoms, (14) and rarely for prophylaxis, although there are some case reports in the literature showing the successful use of homeopathic drugs

for prophylaxis of epidemic disease. (15,16)

Dietary supplements include an array of substances, including vitamins, enzymes, herbs and functional foods. (17) Thus clinical use of dietary supplements is highly variable. In fact, in the U.S., the class is restricted to so-called "structure-function" claims, limiting claims to those that cause the body to maintain "healthy function". (17) In practice, dietary supplements routinely make claims that could easily be interpreted as either structure-function claims or drug claims and are de facto used to treat symptoms. For example, the dietary supplement structure-function claim, "helps the body maintain natural sleep" and the drug claim "sleep aid" are 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 domain of symptom relief.

The regulatory difference among allopathic drugs, homeopathic drugs and dietary supplements is no less complicated. Figure One shows a comparison of regulation of the three categories. For ease of discussion, it is helpful to contrast controlling law, pre-market approval, post-market regulation (manufacturing, marketing and sales), advertising regulation and reimbursement status for the three types of products.

Allopathic drugs are governed by the Federal Food, Drug and Cosmetic Act (FDCA) and related regulations, principally Title 21 of the Code of Federal Regulation (21CFR). Pre-market approval is through the New Drug Application (NDA) process for new drugs, while certain non-prescription drugs (OTCs) that have been grandfathered in due to a long history of use are subject to the FDA OTC review. Post-market regulation is principally specified in 21CFR and includes Good Manufacturing Practices (GMPs) and adverse event reporting. Drug claims are required on labeling. OTC drugs are limited to claims for self-limiting conditions that do not require medical diagnosis or monitoring. (18) Advertising for prescription allopathic drugs is regulated by the FDA, while advertising for non-prescription allopathic drugs is regulated by the Federal Trade Commission (FTC). While reimbursement patterns for allopathic drugs may vary, the general rule is that prescription drugs are reimbursed and may be deducted as a medical expense for federal tax purposes, while OTC drugs are not reimbursable; but are subject to qualifying IRS flexible spending (section 125) plans. (19)

Dietary supplements are not regulated under the FDCA per se, but rather under a supplement to the drug law, the Dietary Supplement Health and Education Act of 1994 (DSHEA). As a result, supplements have no pre-market approval process. Claims must

Figure One. Comparison of regulatory schemas for allopathic drugs, homeopathic drugs and dietary supplements

	Enabling Legislation	Pre-market approval	Good Manufacturing Practices (cGMPs)	Labeling Guidelines	Indications for Use	Advertising Guidelines
Allopathic	FDCA	New Drug Application (NDA)	21 CFR	21 CFR	Required	Rx-FDA; OTC-FTC
Homeopathic	FDCA	HPCUS Monograph Process	21 CFR	21 CFR	Required	Rx-FDA; OTC-FTC
Dietary Supplements	DSHEA	None	Proposed but not finalized	DSHEA	Drug claims impermissible, "Structure-function" claims only	FTC

be reported to the FDA prior to marketing (20) and products may be freely sold unless and until FDA objects. Supplements have become subject to recently promulgated GMPs (21); however, some critics, including the Institute of Medicine (IOM) (22), point out that dietary supplement GMPs are less rigorous than their drug GMP counterparts. Dietary supplements may not make drug claims. Structure-function claims are permissible and are determined to be acceptable if they do not fall into any one of ten categories of drug claims outlined by the FDA. Among those categories are products claiming to have: an effect on a specific disease or class of diseases; an effect on one or more signs or symptoms that are recognizable as being characteristic of a specific disease; an effect on disease through one or more of the following factors: (a) the name of the product; (b) a statement about the formulation of the product, including 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; (c) citation of a publication or reference, if the citation refers to a disease use; (d) use of the term "disease" or "diseased;" or (e) use of pictures, vignettes, symbols, or other means. Also included are products whose claim belongs to a class of products that is intended to diagnose, mitigate, treat, cure, or prevent a disease; or is a substitute for a product that is a therapy for a disease. (23)

Even with the great specificity of regulation developed by the FDA, as previously noted, the line between a drug claim and a dietary supplement claim

can, in many cases, be difficult to determine. Like OTC drugs (but unlike prescription drugs), advertising of dietary supplements is regulated solely by the FTC. Dietary supplements are typically not subject to reimbursement.

By contrast, homeopathic drugs are subject to the FDCA and regulations in 21CFR. Instead of the NDA process, pre-market approval for homeopathic drugs is by way of monograph approval by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS). While homeopathic drugs are subject to the FDA OTC review, the FDA has not acted on homeopathic drugs as of this writing. Manufacturing, labeling, marketing and sales of homeopathic drugs are subject to FDA Compliance Policy Guide 7132.15, "Conditions Under Which Homeopathic Drugs May Be Marketed" (24) (also known as Section 400.400), which, with the exception of provisions for expiration dating, tablet imprinting and finish product testing, are functionally identical to their allopathic counterparts. Good Manufacturing Practices (GMPs) for homeopathic and allopathic drugs are the same. Advertising oversight and reimbursement for homeopathic and allopathic drugs are also identical.

While there are substantial regulatory differences between dietary supplements and drugs generally, the distinction between homeopathic and allopathic drugs specifically falls principally in the manner of pre-market approval. As previously noted, in lieu of the NDA process, homeopathic drugs use a parallel regulatory track through the HPCUS monograph process.

The Homeopathic Pharmacopoeia of the United States

An important element in understanding the regulatory scheme for homeopathic drugs is a clear understanding of the role of the HPCUS. The Homeopathic Pharmacopoeia of the United States (25) 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 the Homeopathic Pharmacopoeia Convention of the United States (HPCUS) was formed as a separate legal entity.(6) HPCUS is a standard-setting organization with particular emphasis on regulatory approval of official homeopathic drug products and development and publication of General Pharmacy practices and Standards and Controls data.

At present there are 1,286 official homeopathic drug products recognized in the HPUS, a publication in excess of 1600 pages.(26) The process by which homeopathic substances are approved and made official homeopathic drug products (HDPs) is shown in figure two.

HPCUS Approval Standards

The Criteria for Eligibility for Inclusion in the HPUS require a homeopathic drug product to be determined by HPCUS to be safe and effective, be prepared according to the specifications of the HPUS General Pharmacy, and comply with one of the following classes:

a. The therapeutic use of a new and non-official homeopathic drug is established by a homeopathic drug proving and clinical verification acceptable to the HPCUS. During the period of clinical verification the drug will be accepted for provisional review and should be available on a monitored basis;

b. The therapeutic use of the drug is established through published documentation that the substance was in use prior to 1962;

c. The therapeutic use of the drug is established by at least two adequately controlled double-blind clinical studies using the drug as the single intervention; or

d. The therapeutic use of the drug is established by: a) data gathered from clinical experience encompassing the symptom picture, pre- and post-treatment, including subjective and any available objective symptoms or b) data documented in the medical literature.(7)

Of these variable criteria (a through d), criterion b, clinical use prior to 1962, was used to grandfather many drugs during the 1970s and 1980s. This criterion is now rarely, if ever, used; and HPCUS is re-reviewing many monographs accepted using this approach. HPCUS reports that criterion "d" has

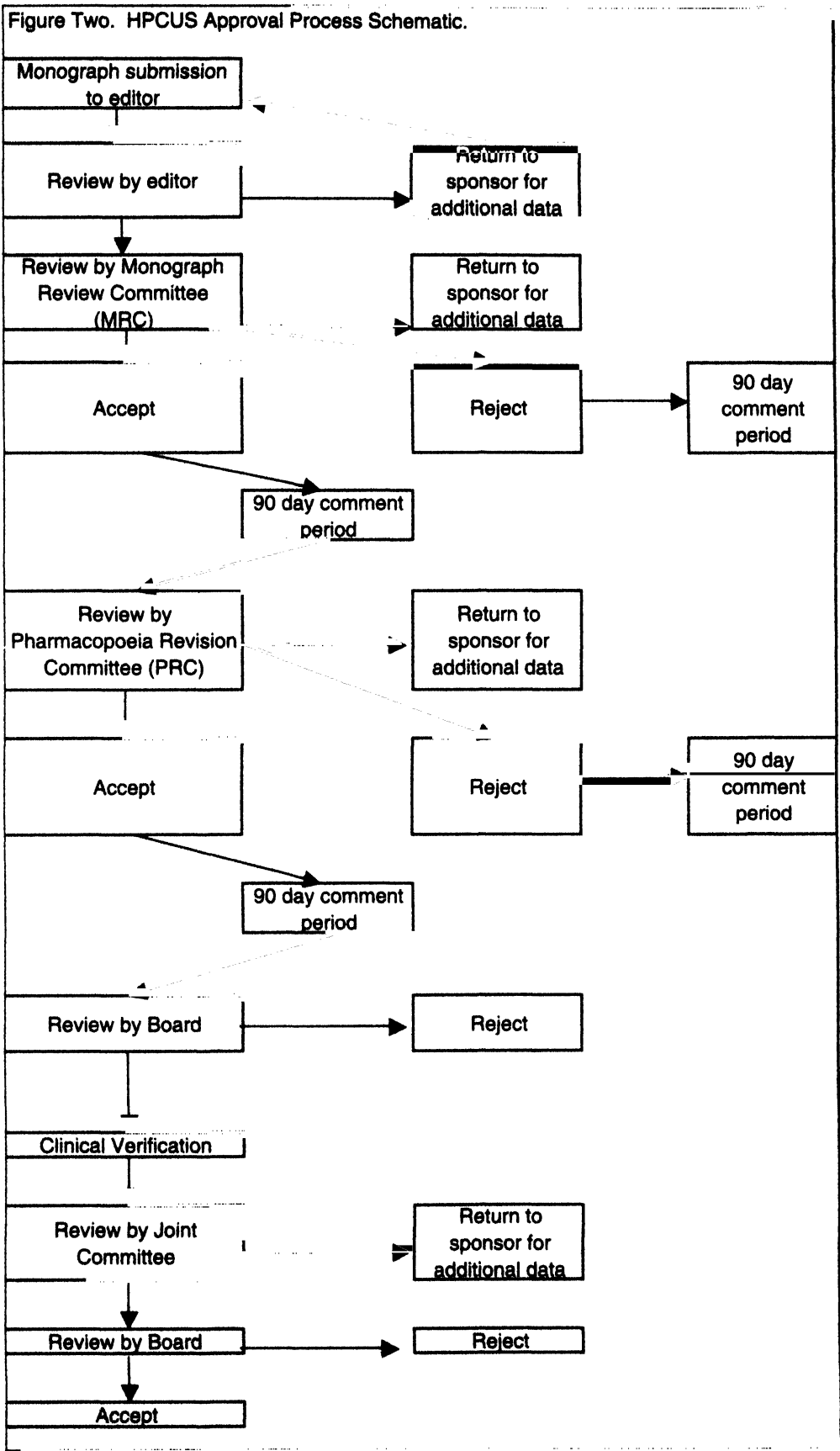
never been used. Consequently only criterion "a" (homeopathic drug provings) and criterion "c" (two adequately designed and well-controlled clinical studies) are currently in use.

Unique to homeopathy, the notion of a homeopathic drug "proving" (27) has its roots directly in the Similia principle. Recall that Hahnemann's technique was to administer a dose of a pharmacologically active substance to a healthy volunteer and note the symptoms that developed. A homeopathic dose of the substance was then administered to an individual afflicted with similar symptoms from a different etiology to determine if the symptoms improved. Modern provings are remarkably similar to Hahnemann's technique. Although methodologies vary, typically a sample population is administered a placebo for a pre-trial run-in period, followed by a study period of exposure to an infra-toxic 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, 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-report, with proper controls the HPCUS will accept proving data. After analysis and acceptance by the HPCUS, the data are then subject to clinical verification - the clinical use of the drug to mitigate symptoms while capturing outcome data using case-series methods.

Criterion "d", adequately designed and well-controlled clinical trials, should be the most recognizable methodology to the reader. Trials of this type have become the norm for homeopathic medicines as well.

The HPCUS Approval Process

The process by which judgments are made concerning monographs begin with submission of a monograph in appropriate form to the HPCUS Monograph Editor. After cursory review for completeness and formatting, the monograph file is forwarded to the Monograph Review Committee (MRC) for first review. MRC is composed principally of basic scientists and pharmacists (non-clinicians) and focuses on the technical aspects of the monograph, including substance characterization, quality analysis and controls, assay techniques and reference reagents, as well as the technical aspects of drug production. MRC will also evaluate all available toxicology data for the substance and determine the appropriate drug potencies for prescription drug application, OTC application and topical application, if appropriate. 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 comment for a 90 day period.

After publication for comment, the monograph along with public comments is presented to the Pharmacopoeia Revision Committee (PRC) for second review. PRC is composed principally of clinicians and concerns itself with the proving or clinical trials data as well as a second review of technical information. Both MRC and PRC review related toxicology and safety data and make recommendations for the dosages at which the drug may be marketed as over the counter or on a prescription-only basis. Like MRC, PRC may request more data, reject or accept. If a monograph is accepted and differences exist between MRC and PRC opinions, a joint MRC-PRC meeting may be called to resolve those differences. After preliminary approval by MRC and PRC, the monograph, along with recommendations, are forwarded to the HPCUS Board of Directors, who act as the final decision-makers. 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 of this data set based on standard criteria of effect size, clinical indications for use and potential toxicity or side-effects of the substance. 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 and made an official drug within the meaning of the FDCA.

One can see that the HPUS monograph process is substantially different than the NDA process of Phase I through Phase III clinical trials. The difference acknowledges the clinical history of homeopathic drugs and the necessity for data collection techniques that are specific to the therapy. The HPCUS monograph process, which has evolved over the last 150 years, is sufficiently robust to produce only a few new homeopathic drugs every decade, but assures the community that those new drugs are safe and evidence-based.

Conclusion

Differences exist between the regulation of homeopathic drug products, dietary supplements and allopathic drugs; but the rationale is the same - safety and effectiveness. It is important for clinicians and policy makers to be aware of these classes of therapeutic goods, their strengths and weaknesses, and the possibilities related to their collective contribution to public health in the United States.

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About the author: Jay Borneman is the Chief Executive Officer of Standard Homeopathic Company, a manufacturer of homeopathic drug products; and receives compensation from them. A7H

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