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Homeopathic Drugs: What Are They, And How Are They Regulated In The United States And In The European Union?

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I. Introduction

Homeopathic drugs have become increasingly popular in recent years, possibly as a result of the renewed interest in the use of natural medicines. Contrary to popular belief, however, homeopathic drugs are not necessarily herbal drugs or natural drugs. Rather, the distinguishing characteristic of homeopathic drugs is that they derive their therapeutic effect from the "Law of Similars." Simply stated, the "Law of Similars" holds that certain disease symptoms may be relieved if patients are given small doses of substances that have been found, at higher dosage levels, to produce similar disease symptoms. In other words, substances that may harm a healthy person when given in large doses may cure a sick person when given in smaller doses.

Ever since the principles of homeopathy were first established in Germany in the late 18th century, homeopathic medicines have been widely used and generally accepted in the mainstream medical community throughout Europe¹, especially in Germany and France. In the United States, however, the acceptance and popularity of homeopathy has fluctuated widely.

Homeopathy was first introduced to the United States in the late 1820s and obtained wide popularity after the Civil War. By 1900, it is estimated that there were over 20 homeopathic medical schools (now there are none) and over 9,000 homeopathic physicians in

the United States. The popularity of homeopathy subsequently waned, however, partially due to the opposition of the American Medical Association (which was founded in 1847 in response to the founding of the American Institute of Homeopathy in 1844).

The primary impetus that led to the virtual demise of homeopathy, however, was the emergence of the allopathic pharmaceutical industry. Allopathic drugs, currently the most widely used drugs throughout the world, produce pharmacological effects that counteract symptoms or diseases. These allopathic synthetic medicines (particularly antibiotics) became increasingly popular in the late 1930s. Subsequently, major national and multinational pharmaceutical companies focused their attention on new classes of allopathic therapeutic agents (e.g., analgesics, oral hypoglycemics, anti-hypertensives, antiemetics, antitussives, diuretics, H₂ blockers, etc.). In the frenzy to produce new allopathic agents, homeopathy was eclipsed and dramatically lost popularity. In fact, it is estimated that by the early 1970s, the entire homeopathic pharmaceutical market in the U.S. comprised less than \$10 million in sales. No medical or pharmacy schools in the U.S. taught homeopathic concepts, and the number of homeopathic physicians decreased dramatically to a few hundred.

During the last 20 years, however, the American public has exhibited renewed interest in homeopathic medications. This interest has been prima-

rily fueled by the demand by consumers for safe "natural" products. A secondary impetus that has led to the renewed interest in homeopathy by consumers was the modification of the federal Food, Drug and Cosmetic Act of 1938 (FDCA)² in 1976, regarding vitamins, minerals and herbal products.

As a result of these developments, it is currently estimated that between \$100-200 million of homeopathic drug products are sold in the United States each year. The 1995 Directory published by the National Center for Homeopathy lists over 500 homeopathic practitioners in the United States.

In 1988, as a result of this recent surge in popularity, the Food and Drug Administration (FDA) began to regulate homeopathic drug products more stringently. If anything, increased regulatory scrutiny has served to benefit the homeopathic pharmaceutical industry since consumers and health professionals have become more aware of the overall positive safety profile of homeopathic drugs.

II. The Founding of Homeopathy — Favorable Safety Profile

The practice of homeopathy was founded by Samuel Hahnemann (1755-1843) in the late 18th century. Hahnemann observed that Cinchona bark (the source of quinine) was an effective remedy for malarial fever. This led him to postulate a method of treatment based upon the concept of

"like cures like" (the Law of Similars). In order to test the theory, Hahnemann conducted an experiment. While healthy, he took large doses of Cinchona bark and observed the results. Hahnemann soon developed the symptoms of malarial fever. From this experiment, Hahnemann opined that the "Law of Similars" was applicable and that the same substance that causes symptoms in a healthy person may relieve such symptoms in an unhealthy person. The seeds of homeopathy were planted.

After further experimentation, Hahnemann and his colleagues soon observed, somewhat surprisingly, that infinitesimal potencies of homeopathic medications (very dilute doses) are more effective than less dilute medications. This powerful conclusion is a fundamental principle of homeopathy and is responsible for the favorable safety profile of homeopathic drugs. There are very few published reports of homeopathic drug adverse events.

Homeopathic drug products therefore appear to be safer than most allopathic drug products. While it is believed that homeopathic drugs stimulate natural defense mechanisms,³ allopathic drugs produce pharmacological effects that counteract symptoms or diseases. Unlike homeopathic drugs, therefore, allopathic drugs cause clearly defined chemical reactions within the body - which are more likely to cause side effects.

III. Basic Principles of Homeopathy

As noted, the essential principle of homeopathy is the "Law of Similars." According to this principle, the same substance that can cause specific symptoms in healthy people may relieve such symptoms if given in a small dose. Homeopathic drugs are therefore tested in "provings" that are designed to see how a substance affects healthy people. For instance, if a substance is found to induce nausea in healthy people when given in large doses, this substance may prevent nausea when given in small doses. Over the years, hundreds of substances have been tested in such "provings."

The second major principle of homeopathy is the principle of the infinitesimal dose. Since homeopathic substances will actually cause symptoms when given in a large dose, it is critical that the substances are substantially diluted before they are given to a patient.

The third major principle of homeopathy is that treatment should be individualized. Homeopaths believe that each homeopathic drug product acts differently in different people. Consequently, homeopathy is premised upon the belief that there is a unique cure for each person. Even though a number of homeopathic medications are typically available to treat a general ailment, each medication will have a different "symptom picture." In order to choose the appropriate homeopathic drug product, one should determine which "symptom picture" best fits one's symptoms.

IV. Preparation of Homeopathic Drug Products

Although homeopathic pharmaceutical companies have slightly different methods for diluting their drug products, the following procedures are indicative of the general approach. First, the base preparation, or "mother tincture," of the homeopathic drug is prepared (which may be derived from plants, animals, and/or minerals). Then, the "mother tincture" is gradually diluted in a solvent (usually water and/or alcohol) and vigorously shaken (causing molecular agitation, or "potentization"). The dilution process is typically repeated a number of times before the homeopathic medicine is ready for use. Over the years, it has been found that a more dilute homeopathic drug is more potent than a less dilute drug. This counter-intuitive result is reflected in the homeopathic dilution terminology. Homeopathic drugs are diluted according to one of two scales: decimal ("X") or centesimal ("C"). Although this sounds confusing, it is relatively easy to understand.⁴

V. Effectiveness of Homeopathic Drug Products

There is no widely accepted scientific rationale that explains how homeopathic drugs achieve their positive effects. Although it has been theorized that homeopathic drugs stimulate innate natural defense systems, the precise mechanism of action for this effect is unknown. Some scientists have speculated that electromagnetic signals or energies are transferred in the diluted homeopathic preparations (retaining a "memory" of the "mother tincture"), thereby triggering responses in the body.

Based upon the absence of a scientific explanation for the effectiveness of homeopathic drug products, some have argued that homeopathy is nothing more than an elaborate "placebo effect." In other words, the critics of homeopathy contend that homeopathic drug products are effective only because patients believe they are effective. These critics believe that patients taking homeopathic drug products would show the same improvement in symptoms if they were given sugar tablets with no active ingredients (placebos).

A number of studies, however, have found that homeopathic drug products are more effective than placebos. In one study, for instance, scientists compared the effects of a homeopathic preparation of mixed grass pollens ("30C") with placebo in 144 patients with hay fever. The scientists found that patients taking the homeopathic preparation showed a greater improvement in symptoms than those taking a placebo.⁵ Similarly, in a separate study, 28 patients with allergic asthma were given a homeopathic drug product ("30C") or placebo. The scientists again found that the homeopathic drug product was more effective than the placebo.⁶

Perhaps the most significant homeopathic effectiveness study was conducted in 1991. Researchers conducted a meta-analysis, reviewing 107 homeopathic drug trials that were printed in 96 published reports. The researchers

found a positive trend: of the 105 trials with interpretable results, 81 trials suggested that homeopathic drugs are effective while 24 suggested they are ineffective. The researchers concluded that although the results of their analysis may be complicated by publication bias, and although a number of trials were of low methodological quality, there nevertheless is evidence in support of the effectiveness of homeopathic drugs.⁷

VI. FDA Regulation of Homeopathic Drug Products

A. Statutory References

Official legal recognition of homeopathic drugs in the United States may be attributed to the principal author of the FDCA, Senator Royal B. Copeland, M.D., a homeopathic physician. The FDCA provides that the term "drug" includes "articles recognized in the official Homeopathic Pharmacopeia of the United States."⁸ Homeopathy therefore receives special status under the FDCA.

Homeopathic drug products are also mentioned in other parts of the FDCA. Section 501⁹ - relating to adulterated drugs - provides in subpart (b) that a drug is deemed to be adulterated [i]f it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium." That subpart also provides that:

Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall be subject to the requirements of the United States Pharmacopeia *unless it is labeled and offered for sale as a homeopathic drug*, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States and not to those of the United States Pharmacopeia. (Emphasis added.)

Section 502 of the FDCA¹⁰ - relating to misbranded drugs - also recognizes the Homeopathic Pharmacopeia of the United States. That section also con-

tains two homeopathic provisos comparable to the language found in Section 501. Accordingly, drugs that are recognized in the official Homeopathic Pharmacopeia are not adulterated when they are manufactured in accordance with Pharmacopeia specifications, nor are they misbranded when they are labeled in accordance with the labeling provisions of the Pharmacopeia.

B. Regulatory Distinctions From Allopathic Drugs

The FDCA defines "drug" to include both homeopathic and allopathic substances. A "drug" is defined as including "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals...and articles (other than food) intended to affect the structure or any function of the body of man or other animals."¹¹ FDA, however, has opted to regulate homeopathic drugs differently than allopathic drugs. FDA has issued a "Compliance Policy Guide" (which is discussed, *infra* Section VI.C) that outlines FDA's method of regulating homeopathic drugs.

Allopathic drugs that are classified as "new drugs"¹² (meaning they have not been widely used and are not generally recognized as safe and "effective") may not be marketed unless they are found by FDA to be both safe and effective. In order for FDA to make this determination, a company must submit, and FDA must approve, a costly "new drug application" (NDA).¹³ These applications contain the results of safety and efficacy studies that support the marketing of a specific drug product. It has been estimated that it costs the allopathic drug industry between \$300-400 million to obtain FDA approval of a new chemical entity "new drug."

A homeopathic drug, on the other hand, may be marketed without FDA making a determination that the drug is safe and effective; homeopathic drugs may be marketed without following FDA's NDA clearance procedures. FDA justifies its regulatory dis-

inction between allopathic and homeopathic drugs upon the relative positive safety profile of homeopathic drugs.

FDA's regulatory distinction between homeopathic drugs and allopathic drugs also extends to its mechanism for regulating the sale of over-the-counter (OTC) drugs (drugs that may be purchased without having to obtain a prescription from a health professional). Under FDA's OTC Drug Monograph System, specific allopathic OTC drug ingredients are reviewed to see whether they are generally recognized as safe and effective for their specific indication. If an allopathic drug ingredient is not listed in a relevant OTC monograph, the ingredient may not be included in an OTC drug unless an NDA is submitted and approved by FDA. Homeopathic drugs, however, are not part of the "OTC Review" and therefore OTC homeopathic drug ingredients do not need to be listed in an OTC monograph.¹⁴

In 1994, a number of physicians and interested parties submitted a formal Citizen Petition¹⁵ to FDA, requesting that FDA regulate homeopathic drugs in the same manner as allopathic drugs.¹⁶ This 2-page Citizen Petition contains 3 exhibits and 42 signatures, but fails to present a coherent argument in favor of a modification in FDA's policy toward homeopathy. Not surprisingly, FDA has not attempted to alter its regulatory position regarding homeopathic drug products based upon this Petition.

C. Homeopathic Drug "Compliance Policy Guide"

At one point in the mid-1970s, FDA dismissed homeopathy as a dying medical practice. Consequently, FDA attempted to remove all of the FDCA's references to homeopathy in a bill known as the "Drug Regulatory Reform Act of 1978." Although this bill passed the Senate, Congress adjourned before final action on the legislation was complete. After realizing the bill was not likely to be passed, FDA reached a compromise with the homeopathic community. FDA agreed

to support the status quo regarding the wording of the FDCA (including the references to homeopathy), but also indicated its intent to establish an official homeopathic policy statement.

In 1988, after 10 years of negotiation with homeopathic physicians, pharmaceutical manufacturers and lay groups, FDA issued a Compliance Policy Guide (CPG) (an official enforcement policy statement) that formally establishes the manner in which homeopathic drugs are regulated.¹⁷ Despite the CPG, homeopathic drugs are still regulated less stringently than allopathic drugs.

The CPG provides that homeopathic drugs may only contain ingredients that are generally recognized as homeopathic. Such recognition is most often obtained via the publication of a monograph in the HPUS.

However, as long as other official documentation exists in support of general recognition, a homeopathic drug ingredient does not necessarily have to be recognized in the HPUS. In recent years, very few new homeopathic ingredients have been added to the HPUS. FDA has also noted that a product's compliance with a HPUS monograph does not necessarily mean that it has been shown to be safe and effective.

According to the CPG, and in accordance with established FDA principles regarding allopathic drugs, a homeopathic drug may only be marketed without a prescription (OTC) if it is intended solely for self-limiting disease conditions amenable to self-diagnosis (of symptoms) and treatment. Other homeopathic drugs must be marketed as prescription products. In addition, if an HPUS monograph states that a drug should only be available on a prescription basis, this criteria will apply even if the drug is intended for a self-limiting condition.

The CPG also provides that FDA's general allopathic drug labeling requirements are also applicable to homeopathic drugs. The labeling requirements for homeopathic drugs include, but are not limited to, the following:

1. Each product must bear the name and place of business of the manufacturer, packer, or distributor;

2. Each product must list all active ingredients, including the level of dilution;

3. Each product must bear an established name, which must be in English but may also be listed in Latin;

4. Each prescription product must contain the following legend: "Caution: Federal law prohibits dispensing without a prescription."

5. Each OTC product must bear adequate directions for use;

6. Each OTC product must bear at least one major OTC indication for use (this requirement has been problematic for the homeopathic industry since single ingredient homeopathic drug products are typically indicated for a "symptom picture" rather than a specific indication-i.e., cough or cold.

Nevertheless, the homeopathic industry has done its best to comply with this requirement. Compliance is easier for multiple ingredient products since the appropriate indication is determined based upon the overlap of the "symptom pictures" of each ingredient).

In addition, all firms that manufacture, prepare, compound, or otherwise process homeopathic drugs must register their drug establishments with FDA and must also "list" their drugs with the agency.¹⁸ The "listing" requirement has been applied in a controversial manner by FDA: the agency has refused to list certain homeopathic drug products if it believes other homeopathic regulatory requirements have not been met. Homeopathic drugs must also be manufactured in conformance with "current good manufacturing practices" (regulatory requirements relating to the methods used in, and the facilities used for, the manufacture of drug products). Due to their unique nature, homeopathic drugs are exempt from FDA's requirements for expiration date labeling.

D. FDA Enforcement Activity and Rule Making Regarding Homeopathic Drug Products

For most of its existence, FDA has been suspicious of the homeopathic pharmaceutical industry and has exhibited a strong anti-homeopathic bias. Since the publication of the CPG, FDA has increased its regulatory scrutiny of homeopathic drug products.¹⁹ FDA has a number of options available to challenge the marketing of homeopathic drug products, including the following three common areas of focus:

1. Ingredient Violations-Homeopathic drug products must contain ingredients that are generally recognized as homeopathic. Otherwise, products may not be marketed as homeopathic. In addition, a product that contains a combination of non-homeopathic active ingredients and homeopathic active ingredients also may not be marketed as homeopathic.²⁰

2. Prescription Labeling Violations-Homeopathic drug products may only be marketed OTC if they are intended to treat a disease or symptom that is self-limiting and amenable to self-diagnosis and treatment by the laity. Consequently, homeopathic drug products that are intended to treat disease symptoms such as cardiac arrhythmias²¹ and lymphatic disorders²² may not be marketed OTC. These products may only be used under the supervision of an appropriately licensed health care professional.

3. Parenteral Homeopathic Drugs-FDA has alleged that homeopathic parenteral (injectable) drug products must be manufactured in accordance with the sterile manufacturing standards applicable to allopathic drugs. FDA has refused to permit the importation of homeopathic parenteral drug products that do not meet these requirements.

There are no special enforcement mechanisms or procedures that apply to homeopathic drug products. If FDA decides to initiate an enforcement action against a homeopathic drug product, it will follow the same enforce-

ment procedures that are used for allopathic drug products. Possible FDA actions include a product seizure, issuance of an injunction, initiation of a criminal action, and, where applicable, border detentions and the refusal of entry into the United States.

The homeopathic pharmaceutical industry has been actively involved in FDA rule making initiatives. For instance, FDA recently issued a final regulation that requires the disclosure of alcohol levels in OTC drugs.²³ Based upon comments submitted by the homeopathic industry, however, FDA agreed that certain labeling requirements will not apply to homeopathic drug products until FDA researches the issue in greater detail and obtains more detailed comments from interested parties. The homeopathic pharmaceutical industry has also claimed an exemption from FDA's tablet imprinting regulations²⁴ for medicated pellets (which are processed without compression, making imprinting impossible).

VII. The Homeopathic Pharmacopeia of the United States

The HPUS was first published in 1897 and is still updated regularly. The HPUS was initially published by the Committee on Pharmacy of the American Institute of Homeopathy and is currently published by the Homeopathic Pharmacopeia Convention of the United States (HPCUS), a private, non-profit entity organized exclusively for charitable, educational, and scientific activities. HPCUS has established a number of committees, including the Council on Pharmacy (COP), which is responsible for making recommendations to the Board of Directors regarding all issues not related to individual monographs.

As noted, the HPUS is an official publication that is cited in the Federal Food and Drug Laws and the CPG. The HPUS contains hundreds of monographs for homeopathic ingredients that have been found by the HPCUS to be both safe and effective. Each monograph contains: the name

of the ingredient, the chemical formula and molecular weight of the ingredient, a description of the ingredient (i.e., color, solubility, toxicity, etc.), preparation requirements, and appropriate dilution levels for prescription and OTC use.²⁵ The HPUS also contains general standards for the preparation of homeopathic drugs.

For safety reasons, the HPUS also requires certain homeopathic drug products to be marketed only via a prescription—regardless of the indicated use of the product. Specifically, those products that utilize toxic "mother tinctures" are usually limited to prescription use at lower levels of dilution.

In order for a drug to be eligible for inclusion in the HPUS, the HPCUS must have determined that the drug is safe and effective, the drug must be prepared according to the specifications of the HPUS, and the submitted documentation must be in the proper format as required by the HPUS.

In addition, the drug must meet at least one of the following four criteria regarding efficacy:

1. The therapeutic use of the drug must be established by a "proving" that is acceptable to HPCUS (this is the most common method used to establish the efficacy of a homeopathic drug product. The homeopathic industry has recently been debating the exact requirements of a "proving");

2. The therapeutic use of the drug must be established through published documentation that the substance was in use prior to 1962 (this grandfather provision was designed to deal with older, well-established homeopathic products);

3. The therapeutic use of the drug must be established by at least two adequate and well controlled double-blind clinical studies using the drug as the single intervention (it was never intended for this option to be extensively utilized by the homeopathic industry—this is the standard approach for establishing the efficacy of allopathic drug products); or

4. The therapeutic use of the drug must be 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 subjected to further verification.

If a company believes a drug should be included in the HPUS, the company may submit a proposed monograph to HPCUS. The monograph is then submitted to the Monograph Review Committee (MRC). The MRC is primarily responsible for reviewing submissions for: 1) nomenclature; 2) biological classification; 3) chemical formulae; 4) molecular weight descriptions; 5) range and habitat for botanicals and zoologicals; 6) dosage levels; and 7) preparation, and classification issues.²⁶ The MRC then recommends that the monograph be approved, deferred, or not approved. MRC recommendations are subject to public comment.

After public comments are received, the Pharmacopeia Review Committee (PRC) convenes. The PRC is responsible for: 1) reviewing MRC recommendations; 2) performing an in-depth review of references; and 3) ensuring the adequacy of the symptom picture and/or proving according to HPCUS guidelines and HPUS eligibility criteria.²⁷ The PRC also makes a recommendation to approve, defer, or not approve the monograph.

If the PRC recommendations concur with the MRC recommendations, the monograph is sent to the Board of Directors for final review. If the PRC and MRC recommendations do not concur, a joint MRC/PRC meeting is held to resolve the differences. The Board of Directors then makes its final decisions, which are recorded in the official minutes of the HPCUS. Approved monographs are published in the HPUS.

VIII. Regulation of Homeopathic Drug Products in Europe

The laws and regulations applicable to homeopathic drug products in Europe are exceedingly complex. This complexity is, to a large extent, a result of the two-tiered regulatory system in Europe.²⁸ European Union (EU) directives apply to all Member States, and each Member State also has its own laws and regulations applicable to homeopathic products.

In addition, some Member States, such as the United Kingdom, France, and Germany, have their own Pharmacopeias that serve similar functions as the HPUS. These Pharmacopeias contain manufacturing and processing requirements, as well as detailed monographs for specific homeopathic ingredients. Because the Pharmacopeias in the various Member States have not been harmonized, the homeopathic pharmaceutical industry must adhere to different requirements in different nations.

This complexity has created difficulties for the European homeopathic industry since the present system does not provide for a centralized approval procedure. Homeopathic drug products are therefore treated differently than technologically advanced medicinal products, which are subject to a new centralized approval procedure coordinated by the European Medicines Evaluation Agency (EMA).²⁹

As a result of this complexity, there has been no attempt in this article to provide a detailed analysis of European laws and regulations applicable to homeopathic drug products. Rather, the following discussion primarily summarizes the principal components of the most recent EU homeopathic directive (Council Directive 92/73/EEC) and outlines aspects of this directive that have been targeted for change by the European Project Group on Council Directive 92/73/EEC (Project Group).³⁰ In addition, as an example of country-specific regulation, this section briefly reviews the general approach used in Germany to regulate homeopathic drug products.

A. Homeopathic Council Directives

1. Background

Prior to 1992, homeopathic drug products were principally regulated in Europe according to Council Directive 65/65/EEC (which was established in 1965) and Council Directive 75/319/EEC (which was established in 1975). Directive 65/65/EEC establishes the general framework for the regulation, and approval, of all medicinal products in Europe. Directive 75/319/EEC supplements the above Directive and is designed to ensure the free movement of proprietary medicinal products throughout Europe. Directive 75/319/EEC authorizes a Member State to prohibit the sale of a medicinal product, including a homeopathic product, if the product is lacking in therapeutic efficacy.³¹ Directive 75/319/EEC also establishes the Committee for Proprietary Medicinal Products (CPMP), which is responsible for giving an opinion as to whether a particular proprietary medicinal product complies with Directive 65/65/EEC.³²

2. Council Directive 92/73/EEC

In 1992, Council Directive 92/73/EEC (1992 Directive) was established in order to provide a simplified mechanism for certain homeopathic drug products to be marketed in Europe. European trade associations, such as Germany's Bundesfachverband der Arzneimittel-Hersteller E.V. (BAH) and its pan-European counterpart, Association Europeenne des Specialites Pharmaceutiques Grand Public (AESGP),³³ were actively involved in the drafting of the 1992 Directive.³⁴ The 1992 Directive does not replace the previous Directives but rather supplements them by permitting a Member State to adopt a simplified registration process. According to this simplified process, the manufacturers of certain homeopathic drug products are not required to prove that their drug product is therapeutically effective.³⁵

Member States are not obligated to establish a simplified homeopathic registration procedure and may continue

to require proof of therapeutic efficacy for all homeopathic products.³⁶ Some Member States, such as Germany, utilized a simplified registration procedure even before the 1992 Directive was enacted.

The Directive distinguishes between homeopathic drug products that contain therapeutic indications (i.e., are labeled to affect certain symptoms or disease states) and those that do not contain such indications. Homeopathic drug products that contain therapeutic indications may not utilize the simplified registration process. Homeopathic products that are not labeled with a therapeutic indication, however, are eligible to use the simplified process.

Specifically, the 1992 Directive provides that a homeopathic medicinal product is only eligible for the special simplified registration procedure if:

1. No specific therapeutic indication appears on the labeling of the medicinal product or in any information relating thereto;

2. The product is administered orally or externally;

3. There is a sufficient degree of dilution to guarantee the safety of the medicinal product. In particular, the product may not contain more than 1 part per 10,000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active principles whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.³⁷

If a homeopathic drug product is subject to the simplified registration procedure (which does not require proof of efficacy), the product must bear required labeling. For instance, the product must contain the scientific name of the ingredients and the labeling must clearly provide that the product is a "homeopathic medicinal product without approved therapeutic indications." The labeling must also contain additional information such as the degree of dilution, method of administration, manufacturer's batch number, etc. A warning advising the user

to consult a doctor if the symptoms persist during the use of the medicinal product is also required.³⁸

According to the European Commission, ten Member States have already transposed the 1992 Directive into national law: Germany, France, United Kingdom, Denmark, Italy, Austria, Sweden, Greece, Spain and Finland. Most Member States are expected to adopt a simplified registration procedure.

3. Project Group Proposals Regarding Directive 92/73/EEC

The Project Group, representing 13 Member States, has made a number of recommendations (which are currently being reviewed and considered) to modify the 1992 Directive, including:

1. The Directive should be modified to permit the use of trade names for homeopathic drug products. Homeopathic products currently must exclusively use the scientific name of their ingredient(s). This requirement is unnecessary since consumers will not be confused if a homeopathic drug product contains a trade name. Furthermore, the requirement may cause confusion with regard to homeopathic products that contain multiple ingredients;

2. The Directive should not limit the use of the simplified registration procedure to orally and externally administered preparations. This limitation unnecessarily prejudices traditional pharmaceutical forms such as injectables;

3. The Directive is being interpreted by some Member States to mean that homeopathic drug products prepared at dilutions lower than 1 part per 10,000 of the mother tincture may not utilize the simplified registration procedure. This interpretation is inaccurate since the restriction was only meant to apply to prescription homeopathic products;

4. The reference to "mother tincture" should be altered to refer to "mother substance." In this manner, insoluble substances will be included;

5. The reference to the "smallest dose used in an allopathic medicine" should be altered to refer to the "usual dose." This change is necessary since it is difficult to determine the actual smallest allopathic dose;

6. The disclaimer, "homeopathic medicinal product without approved therapeutic indications," should not be required since it is unnecessary, redundant, and discriminates against the homeopathic drug industry; and

7. The warning that a user consult a doctor if symptoms persist "during the use of the medicinal product" discriminates against homeopathic drug products. This warning is not required on allopathic drug products and, moreover, there is no correlation between the course of homeopathic treatment and the persistence of symptoms during the use of the product.

B. Brief Overview: Regulation of Homeopathic Drug Products in Germany

According to the German drug law, which was revised in August, 1994, a homeopathic drug product may be lawfully marketed in one of two ways: 1) simplified marketing registration (for products that do not make therapeutic claims);³⁹ or 2) marketing authorization (for products that make therapeutic claims).⁴⁰ Simplified marketing registration is the more common approach, particularly for single ingredient remedies (in which case homeopaths will know how to prescribe the product, and a therapeutic claim is not necessary). However, for multiple ingredient remedies, marketing authorization is the preferred route since the therapeutic use may be unclear even for homeopaths.

The German simplified marketing registration procedure is very similar to the procedure outlined in the 1992 Directive. In fact, the German procedure pre-dates the Directive and was the model on which it was based. As with the 1992 Directive, simplified registration is only available if the homeopathic drug product does not contain a therapeutic indication. However,

the German procedure differs from the 1992 Directive's procedure in that a homeopathic product may use the simplified procedure even if it bears a trade name.

The marketing authorization process is more complex. For drugs that are not new chemical entities, and therefore their effects and side effects are well known (as with the vast majority of homeopathic drug products), "scientific documents" may be presented to the Federal Institute for Drugs and Medical Devices (Institute) (formerly known as the Bureau of Health or BGA) for review. The Institute then reviews these "scientific documents" (which may include clinical trials, articles, "provings," etc.) and may send the documents to one of two Commissions that were established to evaluate homeopathic submissions—Commissions C and D.

Commission C is responsible for reviewing anthroposophic homeopathic drug products,⁴¹ while Commission D is responsible for reviewing all other homeopathic products.⁴² Commission D is primarily responsible for reviewing requests to prolong the marketing authorization of homeopathic products that were on the market prior to January 1, 1978 (when the German Drug Law came into effect). Three members of these Commissions are experts in the field of homeopathy and are responsible for evaluating homeopathic medicines to determine whether they are safe and effective.

The Commissions then provide the Institute with their recommendations. The Institute, however, is under no obligation to follow these recommendations. In recent years, the homeopathic pharmaceutical industry has found it very difficult to obtain marketing authorizations from the Institute. The Institute has established a very high hurdle for scientific documentation, and has therefore kept many products off the market.

IX. Conclusion

For most of the past 40 years, the Institute premised its regulatory position regarding homeopathic drug products

upon the belief that homeopathy is a dying medical practice. In fact, as late as 1978, FDA supported a bill that attempted to terminate the special legal status of homeopathic drug products under the Federal Food and Drug Laws. When the legislative effort failed, FDA began to formulate a regulatory policy that would be applicable to homeopathic drug products. FDA's legislative defeat therefore paved the way for the promulgation of the 1988 Compliance Policy Guide.

The homeopathic market is currently flourishing due to increased consumer demand for safe and effective health products that do not cause side effects. In fact, the homeopathic industry is believed to have grown ten-fold in the last 15 years. Nevertheless, during this period of rapid growth, FDA's enforcement of its homeopathic regulatory requirements has been extremely variable.

In some cases, FDA has legitimately become involved in serious homeopathic industry issues. For instance, it is well known that some companies attempt to introduce illicit and bogus drug products into the marketplace by referring to these products as "homeopathic." These outlaw companies cause significant concern for federal regulators, the homeopathic industry, and consumers. FDA has therefore been actively involved in trying to eliminate this thinly veiled "homeopathic facade."

In other situations, however, FDA enforcement has been questionable. For example, a number of homeopathic border detentions by FDA have appeared to be baseless. These detentions have been grounded more in FDA's general suspicion of homeopathy, rather than in any legitimate regulatory problems. In addition, FDA inspections of homeopathic manufacturing facilities have been particularly demanding in recent years and have been followed by unreasonable demands for manufacturing and/or labeling changes.

FDA has also refused to list certain homeopathic drug products, even though FDA's "listing" regulations do

not appear to authorize this practice.³³ In addition, in some instances FDA has delayed the issuance of "certificates of free sale" (documenting compliance with U.S. regulations) for over a year. FDA uses the request for a "certificate of free sale" as an opportunity to scrutinize homeopathic labeling and other regulatory requirements. These actions may be indicative of FDA's long-standing bias against homeopathic products.

As demonstrated by the above actions, it is unlikely that the chasm of suspicion between the homeopathic industry and FDA will be bridged unless both parties deal rationally with regulatory problems created by the rapid growth of homeopathic drug products in the United States.

In Europe, even though homeopathic drug products are more widely accepted, regulatory issues are still in a state of flux. Confusion appears to result from the lack of harmonization between Member States, as well as the difficulty in applying recently enacted Council Directives.

In the United States and Europe, homeopathic drug products are subject to a constantly changing stream of regulatory requirements. The homeopathic pharmaceutical industry is still learning how to navigate this stream in an effective manner. Future developments will assuredly lead to further regulatory changes, but it is unclear whether the tide will change for the better or worse.

Endnotes

1. According to a 1990 survey, 45% of the general practitioner physicians in the Netherlands believe homeopathic remedies are effective in treating hay fever. Knipschild, et al., Belief in the Efficacy of Alternative Medicine Among General Practitioners in the Netherlands, 31 Soc. Sci. Med. 625 (1990).

2. Pub. L. 94-278, Title V, 90 Stat. 401 (1976), codified at 21 U.S.C. § 321 et seq.

3. Homeopathic stimulation of natural defense mechanisms is distinguishable from the antibody/antigen re-

sponse that results from allopathic vaccine immunization. Homeopathic drugs do not generate an antibody/antigen response.

4. The Homeopathic Pharmacopeia of the United States (HPUS or Pharmacopeia), the primary legal and scientific homeopathic source document [discussed in greater detail, *infra* Section VII], places homeopathic products into specific classes. Depending upon the class, the dilution method may differ. For example, Class E products (homeopathic tinctures of zoological substances) are prepared by dissolving the zoological substance in an alcoholic vehicle. Class F products (triturations of solid substances) are prepared by triturating the dry crude substance with lactose. Special classes have also been established for: (1) nosodes (Class I - attenuations of pathological organs or tissues); (2) allersodes (Class J - attenuations of antigens); (3) isodes (Class K - attenuations of substances that have been ingested or absorbed by the body that are believed to have produced a disease or disorder that interferes with homeostasis); and (4) sarcodes (Class L - attenuations of wholesome organs, tissues, or metabolic factors obtained from healthy specimens).

5. Reilly, et al., Is Homeopathy a Placebo Response? Controlled Trial of Homeopathic Potency, With Pollen in Hay Fever as Model, 2, Lancet 881 (1986).

6. Reilly, et al., Is Evidence for Homeopathy Reproducible?, 344 Lancet 1601-1606 (1994).

7. Kleijnen et al., Clinical Trials of Homeopathy, 302 Brit. Med. J. 316 (1991).

8. FDCA § 201(g)(1)(A), 21 U.S.C. § 321(g)(1)(A).

9. FDCA § 501, 21 U.S.C. § 351.

10. FDCA § 502, 21 U.S.C. § 352.

11. FDCA § 201(g)(1), 21 U.S.C. § 321(g)(1).

12. FDCA § 201(p), 21 U.S.C. § 321(p).

13. FDCA § 505, 21 U.S.C. § 355.

14. 37 Fed.Reg. 9464, 9466 (May 11, 1972) (Because of the uniqueness of homeopathic medicine, the Commissioner has decided to exclude homeopathic drugs from this OTC drug review").

15. Any interested party is entitled to request that FDA take certain action in the future. Such a request is known as a Citizen Petition. 21 C.F.R. § 10.30.

16. The Petition (94P-0316) was submitted on August 31, 1994.

17. CPG 7132.15 (May 31, 1988).

18. 21 C.F.R. Pt. 207.

19. Prior to the publication of the CPG, importers, manufacturers and distributors were subject to inconsistent FDA enforcement ranging from total indifference to active border blockages, seizures and criminal actions.

20. See, e.g., Warning Letter issued to L.B.L. Bot. Bio. Hom. Corp. (April 29, 1994).

21. See, e.g., Warning Letter issued to King Bio Pharmaceuticals, Inc. (October 8, 1992).

22. See, e.g., Warning Letter issued to Nutrition Express Company (October 22, 1993).

23. 60 Fed.Reg. 13590 (March 13, 1995).

24. 21 C.F.R. §§ 206.7 and 207.25.

25. Both homeopathic dilution scales increase logarithmically. A preparation that is designated "1X" means it contains 1 part "mother tincture" and 9 parts solvent. A "1C" preparation contains 1 part "mother tincture" and 99 parts solvent (which

is the same as a "2X" preparation). Some homeopathic medicines are prepared at "24X" (or "12C") when, according to the laws of physics, there is no measurable amount of the "mother tincture" left in the medicine at all. Nevertheless, these "24X" preparations are considered far more potent than "1X" preparations.

26. HPCUS Procedure Manual - Rev. 6/93.

27. Id.

28. For a discussion of the new European drug approval system, see Helmanis, Labeling Within the European Community's New Marketing Authorization System, 12 Food, Drug, Cosmetic and Med. Device L. Dig. 12 (1995) (NYSBA).

29. The EMEA was established in January, 1995 by Council Directive 2309/93/EEC. This Directive was designed specifically for technologically advanced medicinal products such as products derived from biotechnology.

30. The Project Group represents the homeopathic industry in Austria, Belgium, Denmark, Germany, Greece, France, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

31. Council Directive 75/319/EEC, Article 28.

32. Council Directive 75/319/EEC, Chapter III.

33. AESGP is known in the United States as the "European Proprietary Medicines Manufacturer's Association."

34. In Europe, trade associations have a more formal function than they

have in the United States, i.e., to act as formal liaisons to the government.

35. Council Directive 92/73/EEC, Article 4.

36. Council Directive 92/73/EEC, Article 6.

37. Council Directive 92/73/EEC, Article 7.

38. Council Directive 92/73/EEC, Article 7.

39. German Drug Law, § 38.

40. German Drug Law, § 21.

41. Anthroposophic homeopathic drug products are single-ingredient and multiple-ingredient remedies that are formulated based upon an understanding of the "essential nature" of a remedy and its similarity to "formative influences" ultimately responsible for conditions of illness or imbalance.

42. Commission D is primarily responsible for reviewing request to prolong the marketing authorization of homeopathic products that were on the market prior to January 1, 1978 (when the German Drug Law came into effect).

43. 21 C.F.R. Pt. 207.

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