

AMERICAN ASSOCIATION OF



HOMEOPATHIC PHARMACISTS

0152 '99 APR 22 P1:42

Mr. Mike Benson
Food And Drug Administration (HFA-305)
5630 Fisher's Lane, Room 1061
Rockville, MD 20852

Re: Elemental Mercury in Homeopathic Products

April 20, 1999

Dear Mr. Benson,

In response to the Federal Register Announcement (December 14, 1999 – 63 Fed. Reg. 68775), the American Association of Homeopathic Pharmacists (A.A.H.P.) submits the following background information. This information is intended to help Agency personnel understand, *in an appropriate context*, the submissions from individual companies for homeopathic products.

The American Association of Homeopathic Pharmacists was established in 1923 and includes membership from over seventy per cent of the manufacturing and distributing companies in the homeopathic industry. A not-for-profit association, the A.A.H.P. represents the interests of homeopathic drug manufacturers and pharmacists.

In addition, the A.A.H.P. presents *Compliance Through Education* seminars for industry personnel. This is part of the organization's mission: to help all manufacturers and distributors market high quality homeopathic drugs which are in compliance with all applicable federal and state regulations. During the past 3 years, the A.A.H.P. has sponsored seminars on Understanding the cGMPs, and Quality Control/Quality Assurance, both taught by the Center for professional Advancement, as well as a hands-on workshop on Alcohol Drawback and

98N-1109

C4

Regulations, led by personnel from the Bureau of Alcohol, Tobacco and Firearms. This year we will be hosting a weekend seminar and workshop on OTC Homeopathic Drug Labeling and Advertising Regulations.

It is our belief that by working together with regulatory agency personnel, we can help you and your colleagues understand and appreciate the unique place that homeopathic medicines hold in the American medical field. With its long history of safe use, homeopathic medicines stand at the forefront of the complementary and alternative medicines which Americans are increasingly seeking.

BACKGROUND

HISTORY OF HOMEOPATHY

The term "homeopathy" is derived from the Greek words homeo (similar) and pathos (suffering or disease). The first basic principles of homeopathy were formulated by Dr. Samuel Hahnemann in the late 1700's. The practice of homeopathy is based on the experience that disease symptoms can be cured by small doses of substances which produce similar symptoms in healthy people.

Dr. Hahnemann's discovery of homeopathic principles was stimulated by his research on cinchona bark in treating malaria. He found that the ingestion of cinchona bark produced a symptom profile that matched malaria. Hahnemann then began to systematically dilute cinchona and administer it to individuals with malaria, and found that in the vast majority of cases, the diluted remedy was still effective in alleviating malaria symptoms.

Over the next ten years, Hahnemann researched the symptom profiles of a large number of plants using healthy individuals. He recorded the findings and named this process a **proving** (1), a test of the effects of a substance on a healthy person. When someone became ill, Hahnemann conducted physical exams and questioned the individual thoroughly about their general health, outlook on life and the symptoms they were experiencing. Hahnemann then matched the patient's symptoms to the symptom pictures or "provings" and administered a dilution of the matched compound. He called this "*Similia similibus curantur*" or "Likes are cured by likes."

¹ From the German: *Prufung*, which means test or experiment.

This is also referred to as **The Law of Similars**:

- Any pharmacologically active agent will create a characteristic set of symptoms when administered to healthy individuals (i.e. the results of a proving).
- Individuals who are ill will display a specific set of symptoms; these symptoms are the expression of their illness or disease.
- Administration of the “similar” medicine to the sick patient will initiate a curative response.

BASIS OF HOMEOPATHIC PRACTICE

From a homeopathic point of view, symptoms are an expression of the internal curative process which the body goes through to recreate a state of health from a state of “dis-ease”. A cure occurs with the disappearance of some or all of the symptoms by the use of an agent with a toxicology profile (proving) that matches the symptoms of the person who is ill. The curative agent is given in an appropriate dilution to effect the safest cure without aggravating or intensifying the pre-existing symptoms. Hahnemann knew that giving even small doses of toxic substances could have deleterious effects, so he developed a system of dilution that will be explained in the next section. By this method, he found that he could take advantage of the curative properties of an agent without causing any side effects.

In his book dedicated to research work on this similarity phenomenon, Walter A. Heiby documents this activity in nature (2). **Hormesis** is the process of diluting toxins to concentrations of only a few parts per million, or even less, in order to stimulate the body’s ability to metabolically cope with toxins more effectively and to improve enzyme function and extend life.

The **Arndt-Schulz law** of pharmacology states:

- Small or minute doses stimulate enzyme function over time.
- Moderate doses inhibit enzyme function over time.
- Large doses block enzyme function on enzyme substrates over time.

Many of the concentrations used in homeopathic drugs may at first glance seem to be so dilute as to have no possible physiological effect. But it can be helpful to put these concentrations in perspective by comparing them with the normal

² Heiby, Walter A. *The Reverse Effect: How Vitamins and Minerals Promote Health and Prevent Disease*. Deerfield, IL. MediScience, 1st edition, 1998.

concentrations of specific substances in our bodies. Ion concentrations in lymphatic fluid and serum are typically 10^{-3} g/ml. Hormone concentrations range from 10^{-6} to 10^{-18} g/ml depending upon the hormone and the tissue where it is being measured. From this, one can say that most of the lower homeopathic potencies correspond with the natural physiological concentrations found in the body (3). Higher homeopathic potencies (which correspond to extremely low concentrations) utilize mechanisms for their actions which are not yet understood. While controversy surrounds the effectiveness of high dilutions, there is research which indicates that these very highly diluted solutions *do* have physiological effects on a variety of natural systems.

This concept of using toxins in dilutions to stimulate positive biological activity is well defined by the Arndt-Schulz law. Studies have supported the use of toxins in parts per million (and in higher dilutions) to strengthen the body's ability to deal with toxins. One possibility is that homeopathic dilutions assist the body to reactivate enzyme and endocrine systems by interacting with regulatory and biofeedback mechanisms. Many homeopathic concentrations are in the proper range for interacting with the receptor sites at the level of cellular membranes, enzymes and neural synapses.

A number of theories have been attached to homeopathy in an attempt to explain how these dilute solutions work. The effects of homeopathy can be clinically very clear and evident and the physiological changes that homeopathic remedies create in the body can be measured. Some health care professionals identify homeopathic action with the concept of allergy desensitization, or in the similarity to vaccination procedures. However, there is much more to discover about the mechanism of action of homeopathic drugs. The concept of similarity, however, does make it possible to understand the use of homeopathic medicines.

LEGAL BASIS OF HOMEOPATHY

Homeopathic products are drugs as defined for legal and regulatory purposes, and may be either prescription or nonprescription products. They are covered by the original Federal Food Drug and Cosmetic Act of 1938 (FFDCA). As with other over-the-counter drugs, OTC homeopathic medicines must have a drug claim for self-limiting, self-diagnosable conditions on the drug product label.

³ This is similar to the dilution of many allopathic drugs when ingested: a 75kg person ingesting a 0.25 mg dose of digoxin is approximately 10^{-8} g drug per ml of body tissue.

Manufacturers of homeopathic drugs must register with the FDA as drug manufacturing establishments and, in many states, must obtain a state manufacturing license. Those establishments which compound for prescriptions must acquire a state pharmacy license. The FDA regularly inspects manufacturing sites by using the same criteria for evaluation that is used for allopathic drug manufacturers. All stages of manufacturing are regulated under the Good Manufacturing Practices (GMP) of the Code of Federal Regulations (CFR). Manufacturers must comply with provisions of the CFR including Tamper Evident Packaging, the Drug Listing Act and the FDA Compliance Policy Guide – *Conditions Under Which Homeopathic Products May Be Marketed*.

HOMEOPATHIC PHARMACOPOEIA OF THE UNITED STATES (HPUS)

The **Homeopathic Pharmacopoeia of the United States (HPUS)** has been an *official* compendium, along side the U.S.P./N.F. since 1938, by its inclusion in the FFDCa of 1938. If a drug appears in both pharmacopoeias, it is subject to the requirements of the United States Pharmacopoeia (USP) unless it is distinctly marketed, labeled and offered for sale as a homeopathic drug. In this case, it is subject to HPUS requirements.

The HPUS was first published in 1897 and is currently updated through a Revision Service. The Revision Service is published by the **Homeopathic Pharmacopoeia Convention of the United States (HPCUS)**, a private, not for profit organization developed exclusively for charitable, educational and scientific activities. The HPCUS is made up of pharmacists, physicians, lawyers, biochemists, botanists and other professionals. The HPCUS consists of several committees to guide the future direction of homeopathic medicine.

The HPUS contains general standards for the preparation of homeopathic drugs as well as for quality control testing and evaluation. For a drug to be eligible for inclusion in the HPUS, the HPCUS must determine its safety and efficacy with an extensive review of all available documentation by several committees of the Convention. Of course, it must be manufactured according to HPUS standards. The HPCUS determines at which dilution level the agent should be available on a nonprescription or prescription basis.

GMP standards require that all drug manufacturers perform inspection, testing of package components and validation for all production processes. With regard to homeopathy, there are, however, two exemptions. There is no requirement for

assay of the final ingredient in the dosage form. This is because there are such small quantities present in the final product that testing is impossible in most cases. Also homeopathic drugs are not required to undertake expiration date testing, due to the small amount of active ingredient present. The HPUS has additional GMPs which are specific for the manufacture of homeopathic drug products.

HOMEOPATHIC MANUFACTURING

For a proper understanding of the information requested by the FDA, some background information on the manufacturing technology is essential. Since the focus of this submission is homeopathic drug products containing mercury and mercury salts, only these products will be discussed. For other types of homeopathic starting materials (i.e. botanical or zoological in origin), detailed instructions are given in the HPUS.

The starting inorganic mercury salt (4) is identified using validated I.D. tests, similar to those in the USP/NF. A certificate of analysis may also be utilized, when appropriate. The salt is then completely dissolved in solvent/diluent (5) in a ratio of 1 part salt to a total of 10 parts solution. The process of homeopathic attenuation is composed of two important steps. The first is the dilution of the starting material and the second is the vigorous mixing or "succussion" required

⁴ The following monographs in the HPUS contain mercury, and have been designated for OTC sale at the 6X potency [with 2 exceptions]:

Aethiops antimonialis	Mercurius cyanatus [8X]	Mercurius praecipitatus ruber
Aethiops mercurialis-mineralis	Mercurius dulcis	Mercurius Solubulis
Mercurius aceticus	Mercurius iodatus flavus	Mercurius sulphocyanatus
Mercurius auratus	Mercurius iodatus ruber	Mercurius sulphuratus ruber [4X]
Mercurius bromatus	Mercurius methylenus	Mercurius sulphuricus
Mercurius corrosivus	Mercurius nitricus	Mercurius vivus (Quicksilver)
Mercurius cum kali iodatus	Mercurius praecipitatus albus	

⁵ Solvents specified in the H.P.U.S. include water, ethanol, and glycerin. Each individual monograph stipulates the concentration of the hydro-alcoholic diluent to be used for the initial step.

with each dilution step (see below). The resulting solution is labeled as the **1X** dilution (6).

To manufacture the **2X** dilution, one part of the **1X** solution is mixed with 9 parts of the diluting solution, and then succussed. The **3X** dilution is made from 1 part of **2X** dilution plus 9 parts of diluting solution, and succussed. This rhythmic dilution and succussion is repeated as many times as necessary.

The process of shaking the liquid (mixing) with sufficient impact at each stage of the dilution is called **succussion**. Both parts of the manufacturing process are important: the dilution ratio and the activity of succussion. The process of succussion is believed to release the energy of the substance and is used to **potentize** the mixture. It is from this observation that the word "potency" is derived. It is believed that succussion gives a drug its "potency" for that dilution. Depending on the amount of similarity of symptoms and the

⁶ The designation "X", the roman number 10, represents this one-in-ten dilution. This is a **decimal** potency (which is also identified by the letters "D" or "DH"). In homeopathic nomenclature the number which precedes the "X" indicates the number of times it has been subjected to the dilution and succussion process. Therefore, a 12X dilution has gone through the one-in-ten dilution and succussion a total of 12 times.

Another homeopathic designation that is often seen is "C" (or "CH" or "CK"). This signifies a **centesimal** potency. The designation "C", the Roman numeral for 100, represents dilutions which are manufactured by mixing one part of the starting material in 100 parts of the diluting solution. Each subsequent dilution is also made according to the 1:100 ratio. So a 6C dilution has gone through the one to a hundred dilution and mixing a total of 6 times.

The following chart provides some common homeopathic potencies and their corresponding concentrations:

<i><u>Decimal</u></i>	<i><u>Centesimal</u></i>	<i>mg of Starting material / <u>mg dose</u></i>
1X		10^{-1}
2X	1C	10^{-2}
3X		10^{-3}
4X	2C	10^{-4}
5X		10^{-5}
6X	3C	10^{-6}
7X		10^{-7}
8X	4C	10^{-8}
9X		10^{-9}
10X	5C	10^{-10}
24X	12C	10^{-24}
200X	100C	10^{-200}
400X	200C	10^{-400}

application of the drug, various potencies may be prescribed for symptom relief.

For substances that are insoluble in alcohol and water, the attenuation process is accomplished by trituration of the substance with lactose. In this case, the insoluble substance is "diluted" with 9 (or 99) times its weight of lactose. The weight/weight repetitive dilutions are carried out in the decimal or centesimal dilution. This trituration process is repeated until the drug has been diluted to at least a 6X or 3C potency. At this point, the substance is now sufficiently diluted to allow solubility in a fluid medium, and the process may continue to the desired potency.

Once the desired dilutions are made, they may be processed into a variety of dosage forms including:

- | | |
|----------------|-----------------|
| - Tablets | - Suppositories |
| - Pills | - Injectables |
| - Granules | - Creams |
| - Liquids | - Ointments |
| - Nasal sprays | - Gels |
| - Eye drops | - Syrups |
| - Lozenges | - Capsules |

These dosage forms are prepared in much the same way as allopathic drugs. The various dosage forms utilize the same excipients and preservative systems as found in conventional, allopathic drugs. Special dosage forms, including nasal sprays, eyedrops and parenterals are manufactured using the same processes, standards, and G.M.P.s as allopathic drugs.

MERCURY TOXICITY

Quicksilver and mercury salts are considered highly toxic (7). Amounts of 30 μ g of mercury / liter of blood may be toxic.

Yet, in order to effectively consider the potential toxicity of homeopathic drugs which contain mercury, it is imperative to consider *actual use*. The EPA has set Maximum Allowable Levels for mercury content in drinking water; the M.A.L. is 0.002 mg / liter (2 ppb).

⁷ J. Arena, M.D. & R. Drew, R. Ph., *Poisoning: Toxicity, Symptoms, Treatment* 5th Edition (Springfield, Ill.: Charles C. Thomas, Pub., 1986)

R. Baselt, Ph.D. & R. Cravey, B.S., *Disposition of Toxic Drugs and Chemicals in Man* 3rd Edition, (Chicago, Ill.: Yearbook Medical Publishers, 1989)

This level is based upon the correct assumption that large amounts of water will be consumed daily, both in drinking and cooking, on a continual basis over months and years. This means that the exposure to mercury must be considered over longer periods of time, in addition to acute ingestion of large amounts of mercury. As mercury is known to accumulate in the tissues, it is important to limit the daily exposure to mercury in drinking water supplies. A single glass of water may not be problematic, but the long term exposure – with its attendant tissue accumulation – can be a source of concern.

However, this assumption, and its attendant concern, is *inappropriate* when applied to the use of homeopathic medications, which are used in extremely small amounts and for limited time periods. The typical dose of a liquid homeopathic drug is only 7-15 drops (0.3-.75 ml); tablets with an average weight of 250 mg, are usually taken singly. The normal dose of pellets – perhaps the most common homeopathic dosage form is even less – is about 100 mg. A characteristic course of treatment consists of 1 - 3 doses per day over a limited number of days (7-28), with the total amount of homeopathic **attenuation** used in the course of treatment ranging from 0.7 g to 55 g (8).

The margin of *safety* for homeopathic medications is well demonstrated:

A typical dose (anywhere from 0.1 g – 0.75 ml) of a homeopathically prepared 6X mercury salt (9) contains from 0.000066 to 0.000495 mg of elemental mercury. These figures are well below the Maximum Allowable Levels for mercury in drinking water as per EPA guidelines. In fact, these figures are less than the M.A.L. by a factor of at least 20 . Since most of the homeopathic medications on the American market are diluted by factors of 100 or 10,000 or even more than a 6X attenuation, the relative margin of safety grows geometrically with each subsequent attenuation.

Another potential area of concern is the physiological tissue damage which can result from direct contact of mercury or mercury containing salts with the mucosal

⁸ $0.1 \text{ g} \times (1 \text{ dose/day}) \times (7 \text{ days}); 0.75\text{ml} \times (3 \text{ doses/day}) * (28 \text{ days}) * .85$ [average specific gravity]

⁹ The figures presented are for the most concentrated homeopathic mercury products available for OTC sale. It is to be understood that the vast majority of homeopathic mercury products are in concentrations of 100 to 10,000 (or more) times more dilute! The calculations take into account that elemental mercury is approximately 66% of the weight of the mercury salts commonly used in homeopathic medications.

lining of the digestive tract. This is a particular concern following accidental ingestion of mercury. However, this problem occurs when "crude" mercury is present in substantial amounts. The total amount of mercury in a typical dose of a homeopathic 6X mercury salt (see preceding paragraph) is far below the amount which can possibly cause such physical damage to the mucosal tissue. To date, we are *unaware* of any reports of toxicity or tissue damage due to the use of homeopathically prepared mercury containing drug products (10). With a 200 year history of use, the *safety* of these products has been *well established*.

CONCLUSION

The quantity of mercury or mercury salts ingested from a homeopathic product falls well below the E.P.A. acceptable limits for mercury in drinking water. A cursory glance of the HPUS might raise questions because of the number of monographs which indicate the use of attenuated mercury salts. However, a more in depth understanding of homeopathic manufacturing, the homeopathic attenuation process and the actual use of homeopathic medications reveals that homeopathic drug products have a *wide margin of safety* and are not a cause for concern vis-a-vis potential mercury toxicity.

Submitted on behalf of the membership of the American Association of Homeopathic Pharmacists.

A handwritten signature in black ink, appearing to read "Eric L. Foxman". The signature is fluid and cursive, with a large, sweeping flourish at the end.

Eric L. Foxman, R.Ph.

Secretary

¹⁰ The information presented in this submission is based upon those active ingredients which have been prepared according to the homeopathic attenuation process. The A.A.H.P. is not submitting information regarding other components, including the use of mercury containing preservatives, which might be used in homeopathic drug products.

DOMESTIC USE ONLY

2 LB. PRIORITY MAIL
POSTAGE REQUIRED

FOR PICKUP CALL 1-800-222-1811



**PRIORITY
MAIL**

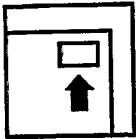
UNITED STATES POSTAL SERVICE™

www.usps.gov

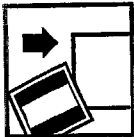
HOW TO USE:



- 1. COMPLETE ADDRESS LABEL AREA**
Type or print required return address and addressee information in customer block (white area) or on label (if provided).



- 2. PAYMENT METHOD**
Affix postage or meter strip to area indicated in upper right hand corner.



- 3. ATTACH LABEL (if provided)**
Remove label backing and adhere over customer address block area (white area).

*Foxman American Association
of Homeopathic Pharmacists
3741 MITFORD Lane
CLINTON WA 98236*

*Food & Drug Administration (HFA-305)
5630 Fishers Lane Room 1601
Rockville MD 20852*

ATTN: Mike Benson.

The efficient FLAT RATE ENVELOPE.

You don't have to weigh the envelope... Just pack all your correspondence and documents inside and pay only the 2 lb. Priority Mail postage rate.

We Deliver.