Drug Products Labeled as Homeopathic
Guidance for FDA Staff and Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact the Center for Drug Evaluation and Research (CDER) at 301-796-2089 or the Office of Communication, Outreach and Development (CBER), 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
Compliance

Revision 1

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance describes how we intend to prioritize enforcement and regulatory actions for homeopathic drug products[2] marketed in the United States without the required FDA approval. As discussed below, FDA has developed a risk-based approach under which the Agency intends to prioritize enforcement and regulatory actions involving certain categories of such products that potentially pose a higher risk to public health.

The Agency anticipates that many homeopathic drug products will fall outside the categories of drug products that FDA intends to prioritize for enforcement and regulatory action as described in section III below.

For the purposes of this draft guidance, we define a "homeopathic drug product" as a drug product that is labeled as "homeopathic," and is labeled as containing only active ingredients and dilutions (e.g., 10X, 20X) listed for those active ingredients in the Homeopathic Pharmacopeia of the United States (HPUS).[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Homeopathy is an alternative medical practice that has a historical basis in theory and practice first systematized in the late 1700s. Homeopathy is generally based on two main principles: (1)

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* and *drug products* refer to human drugs, including drugs that are biological products, regulated by CDER or CBER.

[3] A product that conforms to the HPUS dilution standards may still fall under the enforcement priorities described in section III below.

that a substance that causes symptoms in a healthy person can be used in diluted form to treat symptoms and illnesses (known as "like-cures-like"); and (2) the more diluted the substance, the more potent it is (known as the "law of infinitesimals"). Proponents claim that a significantly diluted aqueous solution, consisting mainly of water molecules, retains therapeutic properties due to a "memory" of the substance diluted in it. Historically, homeopathic drugs have been identified through "provings," in which substances are administered to healthy volunteers in concentrations that provoke overt symptoms. Symptoms experienced by volunteers are recorded to indicate possible therapeutic uses for the substances. In other words, if a substance elicits a particular symptom, individuals experiencing that symptom would be treated with a diluted solution made from that substance.

In 1938, when the Federal Food, Drug, and Cosmetic Act (FD&C Act) was enacted, the bill's senatorial sponsor, Dr. Royal Copeland, himself a homeopathic practitioner, added a provision to the law recognizing the HPUS alongside its counterparts, the U.S. Pharmacopeia (USP) and the National Formulary (NF).[4] Recent years have seen an increase in the sale of homeopathic drug products. In the past, these products were mostly prepared by homeopathic physicians for individual patients. Today they are frequently mass manufactured and widely marketed as over-the-counter (OTC) products.

The definition of "drug" in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)) includes, among other articles, articles recognized in the HPUS or any of its supplements. As such, homeopathic drugs are subject to the same regulatory requirements as other drugs; nothing in the FD&C Act exempts homeopathic drug products from any of the requirements related to approval, adulteration, or misbranding, including labeling requirements. Generally, a drug, including a homeopathic drug, is considered a "new drug" if it is not generally recognized as safe and effective (GRAS/E) by qualified experts for use under the conditions prescribed, recommended, or suggested in the labeling.[5]

FDA makes GRAS/E determinations for OTC drugs marketed under the OTC Drug Review.[6] FDA has not reviewed any homeopathic drug products under the OTC Drug Review, because the Agency categorized these products as a separate category and deferred consideration of them.[7]

Under section 505(a) of the FD&C Act (21 U.S.C. 355(a)), before any "new drug" is marketed, it must be the subject of an approved application filed pursuant to section 505(b) or section 505(j) of the FD&C Act. The requirements in section 505 of the FD&C Act apply to biological products regulated under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262); however, as stated in section 351(j) of the PHS Act, a biological product with an approved license under section 351(a) of the PHS Act is not required to have an approved application under section 505 of the FD&C Act. Accordingly, absent a determination that a homeopathic drug product is not a "new drug" under section 201(p), all homeopathic drug products are subject to the premarket approval requirements in section 505 of the FD&C Act or section 351 of the PHS Act. There are currently no homeopathic drug products that are approved by FDA.

[4] Section 201(g)(1)(A) of the FD&C Act.
[5] Section 201(p) of the FD&C Act.
[6] See 21 CFR part 330.
[7] 37 FR 9464 at 9466 (May 11, 1972).

A. Compliance Policy Guide 400.400

In May 1988, the Center for Drug Evaluation and Research (CDER) issued Compliance Policy Guide (CPG) 400.400 entitled "*Conditions Under Which Homeopathic Drugs May be Marketed.*" As stated in the 1988 CPG, it "delineate[d] those conditions under which homeopathic drug products may ordinarily be marketed," including conditions regarding ingredients, labeling, prescription status, and current good manufacturing practice.

B. FDA's Reexamination of Its Enforcement Policies

In light of the growth of the industry and passage of more than 2 decades since the issuance of CPG 400.400, FDA announced on March 27, 2015, that it was evaluating its regulatory framework for homeopathic drug products.[8] In April 2015, FDA held a public hearing to obtain information and comments from stakeholders about the current use of homeopathic drug products, as well as the Agency's regulatory framework for such products.[9] FDA sought broad public input on its enforcement policies related to homeopathic drug products in an effort to better promote and protect the public health.

Since the issuance of CPG 400.400, the Agency has encountered multiple situations in which homeopathic drug products posed a significant risk to patients. Such products either caused or could have caused significant harm, even though the product labeling and ingredient formulation appeared to meet the conditions of CPG 400.400. For example, in 2016, FDA's search of the FDA Adverse Event Reporting System (FAERS) database identified 99 cases of adverse events consistent with belladonna toxicity, including reports of infant deaths and seizures, possibly related to teething products. Multiple homeopathic drug products were identified as associated with this safety concern. Further investigation revealed that the poisonous belladonna alkaloids in some of the products far exceeded the labeled amounts, raising a serious safety concern. As another example, by 2009, FDA had received more than 130 reports of anosmia (loss of the sense of smell) associated with the use of Zicam homeopathic intranasal zinc products. FDA determined that if the products were used as labeled, a user would receive significant daily exposure to intranasal zinc, raising a serious safety concern.

These are only two examples among many. FDA has also, for example, documented many serious violations of Current Good Manufacturing Practice requirements by manufacturers of homeopathic drug products, raising significant concerns about the safety of the products made with inadequate process controls.

As a result of the Agency's evaluation of its regulatory framework, including consideration of the information obtained as a result of the public hearing and the recent growth of safety concerns associated with homeopathic drug products, FDA believes that it is in the best interest of public health to issue a new guidance that applies a risk-based enforcement approach to

[8] 80 FR 16327, "Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century."

[9] Docket No. FDA-2015-N-0540; available at https://www.regulations.gov/docket?D=FDA-2015-N-0540.

homeopathic drug products marketed without the required FDA approval, consistent with FDA's risk-based regulatory approaches generally.

C. FDA's Risk-Based Approach

In many instances, FDA uses a risk-based approach to carry out its mandates. For example, FDA has generally employed a risk-based enforcement approach with respect to marketed unapproved new drugs.[10] The Agency historically has prioritized compliance actions involving unapproved new drug products that have potential safety risks, lack evidence of effectiveness, are health fraud products, present challenges to the new drug approval or OTC drug monograph systems under the OTC Drug Review, are violative of the FD&C Act in other ways, or are reformulated to evade an FDA enforcement action.

The Agency generally intends to apply a risk-based enforcement approach to the manufacturing, distribution and marketing of homeopathic drug products, as described below.

III. FDA's ENFORCEMENT POLICY

FDA is not required, and generally does not expect, to give special notice that a drug product may be subject to enforcement action. In the listing that follows, we clarify our general approach to prioritizing our enforcement and regulatory actions with regard to homeopathic drug products marketed in the United States without the required FDA approval. However, this guidance is intended to provide notice that any homeopathic drug product that is being marketed illegally is subject to FDA enforcement action at any time.

Enforcement and Regulatory Priorities

In developing a risk-based approach, FDA has identified certain categories of homeopathic drug products marketed without the required FDA approval as potentially posing higher risks to public health. FDA generally intends to prioritize enforcement and regulatory actions with respect to premarket approval requirements involving homeopathic drug products that are marketed without the required FDA approval and that fall within the following categories:

- ***Products with reports of injury that, after evaluation, raise potential safety concerns.*** For example, MedWatch reports or other information submitted to the Agency can indicate or signal a potential association between the product and an adverse event, medication errors, or other safety issues.

- ***Products that contain or purport to contain ingredients associated with potentially significant safety concerns.*** For example, potentially significant safety concerns are raised by products that contain or purport to contain:
    - An infectious agent with the potential to be pathogenic;

[10] See *Marketed Unapproved Drugs - Compliance Policy Guide*, Section 440.100, September 19, 2011. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- A controlled substance, as defined in the Controlled Substances Act, 21 U.S.C. 812;
- Multiple ingredients that, when used in combination, could result in possible interactions, synergistic effects, or additive effects of the various ingredients; and,
- Ingredients that pose a risk of toxic, or other adverse effects, particularly when the ingredients are concentrated or in low dilution presentations (e.g., 1X, 2X, or 1C), or are not adequately controlled in the manufacturing process.

- ***Products for routes of administration other than oral and topical.*** For example, injectable drug products and ophthalmic drug products in general pose a greater risk of harm to users because the routes of administration for these products bypass some of the body's natural defenses. In particular, contaminated injectable and ophthalmic products can pose serious risks to the patient.

- ***Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases or conditions.*** Unapproved products for serious and/or life-threatening diseases or conditions raise public health concerns, in part, because they may cause users to delay or discontinue medical treatments that have been found safe and effective through the new drug application (NDA) or biologics license application (BLA) approval processes.

- ***Products for vulnerable populations.*** For example, patient populations such as immunocompromised individuals, infants and children, the elderly, and pregnant women may be at greater risk for adverse reactions associated with a drug product, even if it contains only small amounts of an ingredient, due to the varying ability of individuals in these populations to absorb, metabolize, distribute, or excrete the product or its metabolites. These populations may also be at greater risk of harm as a result of foregoing the use of medical treatments that have been found safe and effective through the NDA or BLA approval processes or under the OTC Drug Review.

- ***Products with significant quality issues.*** For example, products that are contaminated with foreign materials or objectionable micro-organisms, and/or are made in facilities with significant deviations from current good manufacturing practice, pose a significant safety risk to patients.