Paola Brown
Americans for Homeopathy Choice
1601 18th Street NW
Suite 4
Washington, DC 20009

December 6, 2022

Re: Docket No. FDA 2020-P-1510

Dear Ms. Brown:

This responds to the citizen petition you filed on behalf of Americans for Homeopathy Choice, which was received by the U.S. Food and Drug Administration (FDA or the Agency) on June 5, 2020 (Petition). The Petition requests that FDA take the following actions:

1. Adopt the regulation proposed in the Petition;
2. "Recognize as safe and effective homeopathic drugs that are properly manufactured and labeled and listed in, or formally pending approval for listing in, the Homeopathic Pharmacopoeia of the United States and its supplements and addendums (HPUS)[;]"
3. "Prohibit any drug product not listed in, or formally pending approval for listing in, the [HPUS] . . . from using the term homeopathic in any form that states or implies that the product is homeopathic[;]"
4. "Ensure that any drug product listed in, or formally pending approval for listing in, the [HPUS] . . . is manufactured in accordance with the determinations of the HPUS and the Good Manufacturing Practices of the . . . FDA[;]"
5. "If the FDA applies a risk-based policy to homeopathic drug products and drug products labeled as "homeopathic," ensure that such risk-based policy is formulated and applied with generally accepted standards and procedures of risk assessment[;]" and
6. "[I]f the Agency fails to grant this petition, . . . hold[] a public hearing in accordance with the procedures of the Administrative Procedures [sic] Act (APA) to consider the contents of this petition."

(Petition at 35-36.) FDA has carefully considered the Petition. We have also reviewed the comments in the public docket for this Petition, Docket No. FDA-2020-P-1510. For the reasons described below, the Petition is denied.

I. 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) 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[1] 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 or other dosage form 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 Homeopathic Pharmacopoeia of the United States (HPUS) alongside its counterparts, the U.S. Pharmacopeia (USP) and the National Formulary (NF).[2] 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, including those identified in the HPUS, are subject to the same statutory requirements as other drugs; nothing in the FD&C Act exempts homeopathic drugs from any of the requirements related to approval, adulteration, or misbranding.

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 experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, for use under the conditions prescribed, recommended, or suggested in the labeling.[3] 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. There are currently no homeopathic drug products that are approved by FDA. 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, a biological product with an approved license under section 351(a) of the PHS Act (42 U.S.C. § 262(a)) is not required to have an approved application under section 505 of the FD&C Act.[4] Accordingly, absent a determination that a homeopathic drug product is not a "new drug" under section 201(p) of the FD&C

[1] The Petition states that FDA uses inconsistent terminology in the Revised Draft Guidance by referring to "drug products labeled as homeopathic" in the title and referring to "homeopathic drugs" in the body of the guidance (Petition at p.7, fn6). The Revised Draft Guidance included a definition of "homeopathic drug product" (which is being retained in the final guidance) because various comments to the docket suggested that it would be helpful. Having defined "homeopathic drug product," we used that terminology in the remainder of the revised draft guidance, with the exception of the title. In the final guidance we have conformed the title to refer to "Homeopathic Drug Products".

[2] *See* section 201(g)(1)(A) of the FD&C Act.

[3] *See* section 201(p) of the FD&C Act.

[4] *See* section 351(j) of the PHS Act (42 U.S.C. § 262(j)).

Act, such a homeopathic drug product[5] is subject to the premarket approval requirements in section 505 of the FD&C Act or section 351 of the PHS Act.

Under section 505G of the FD&C Act (as added by the CARES Act[6])—which reforms and modernizes the OTC drug review process established in 1972—FDA now issues administrative orders to make GRAS/E determinations for certain nonprescription drugs marketed without an approved application.[7] Prior to enactment of the CARES Act, FDA had not reviewed any homeopathic drug products under the OTC Drug Review, because the Agency had placed homeopathic drug products in a separate category and deferred consideration of them.[8] Subsequent to enactment of CARES, no GRAS/E determinations will be made for homeopathic drug products under section 505G, because section 505G does not apply to homeopathic drug products.[9] Because at this time no homeopathic drug products have been determined by FDA to be GRAS/E, all homeopathic drug products remain subject to the premarket approval requirements.

A. Compliance Policy Guide 400.400

In May 1988, the Center for Drug Evaluation and Research (CDER) issued Compliance Policy Guide 400.400 entitled *Conditions Under Which Homeopathic Drugs May be Marketed* (CPG 400.400). CPG 400.400 described the Agency's enforcement priorities for homeopathic drugs.

B. FDA's 2017 Draft Guidance

In light of the growth of the industry and passage of more than two 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.[10] In April 2015, FDA held a two-day 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

[5] For purposes of this response, references to *drugs* include biological products as defined in section 351 of the PHS Act (42 U.S.C. § 262). Unless stated otherwise, references to *applications* include both new drug applications (NDA) under section 505 of the FD&C Act and biologics license applications (BLA) under section 351 of the PHS Act.

[6] Public Law 116-136 (March 27, 2020).

[7] In addition, under section 505G(a) of the FD&C Act, certain nonprescription drugs marketed without an approved application are deemed GRAS/E and not new drugs if applicable conditions are met.

[8] *See* 37 FR 9464, 9466 (May 11, 1972).

[9] See section 3853 of the CARES Act.

[10] 80 FR 16327, *Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century*.

for such products.[11] FDA sought public input on its enforcement policies related to homeopathic drug products in an effort to better promote and protect public health.[12]

In determining its path forward, the Agency took into account the fact that there are no approved homeopathic drug products marketed in the United States. Because marketed homeopathic drug products have not been evaluated by FDA for safety and effectiveness, they may not meet modern standards for safety, effectiveness, and quality. Further, although some people assume that homeopathic remedies, which are often marketed as "natural," are unlikely to cause harm the safety of homeopathic drug products (as with all drug products) depends upon many factors,[13] including the manufacturing quality and the identity and amount of the "active" ingredient(s). Some FDA inspections of firms manufacturing homeopathic drug products have identified violations, including significant violations, of current good manufacturing practice (CGMP); the failure to comply with CGMP requirements can cause dilutions that differ from those stated on the labeling and increase the potential for contamination. Although homeopathic drug products are generally labeled as highly diluted, some products contain measurable amounts of active ingredients that could cause significant patient harm. 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 these homeopathic drug 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. Finally, the Agency also recognizes that some homeopathic drug products are marketed to treat serious diseases and/or conditions; as with any unapproved drug product marketed to treat serious diseases and/or conditions, taking such products may also cause harm to consumers who forgo treatment with medical products that have been scientifically proven to be safe and effective.

As a result of the Agency's evaluation, including consideration of the broad and diverse public input and information obtained as a result of the public hearing, FDA issued the draft guidance in December 2017, entitled, "Drug Products Labeled as Homeopathic,

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

[12] The Petition states that the Federal Register notice for this public hearing announced FDA's intention to propose a rule and argues that this process must be completed. This is inaccurate. The notice is titled, "Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century; Public Hearing" and under the heading of "Action," the notice states: "Notice of public hearing; request for comments." The notice nowhere states anything about a proposed rule. Moreover, even if the Agency had indicated an intention to promulgate a rule, it is under no obligation to do so if it determines a rule is not warranted.

[13] See CDER Safety Memo dated October 22, 2019.

Guidance for FDA Staff and Industry." The draft guidance detailed a risk-based enforcement policy, prioritizing enforcement and regulatory actions for certain categories of homeopathic drug products that potentially pose higher risk to public health.

C. FDA's 2019 Revised Draft Guidance

In response to comments received, we revised the draft guidance and reissued it in October 2019 to enable the public to review and comment before it is finalized. In particular, we added a definition of "homeopathic drug product" for purposes of the guidance, added additional explanation of some of the safety issues that contributed to the development of the draft guidance, and clarified the intent to prioritize enforcement and regulatory actions with respect to premarket approval requirements involving homeopathic drug products that are marketed without required FDA approval. Simultaneous with the issuance of the revised draft guidance, FDA withdrew CPG 400.400 because it was inconsistent with the Agency's risk-based approach to enforcement generally and did not accurately reflect the Agency's current thinking.

FDA has reviewed the comments on the revised draft guidance and today is issuing the final guidance, which is substantially similar to the revised draft. The changes made in the final guidance are for clarity and transparency. As part of the process of issuing the final guidance, FDA has taken into consideration this Citizen Petition, the reasoning set forth in this response letter, and the references cited therein. And as part of the process of issuing this response letter, FDA has taken into consideration the comments received on the original and revised draft guidances, the reasoning set forth in the final guidance, and the references cited therein.

II. DISCUSSION

A. Request that FDA Adopt the Draft Rule Proposed in the Petition

The stated purpose of the Petition is to obtain "recognition by FDA that homeopathic drugs, properly manufactured and labeled, and evaluated by appropriate standards, do not meet the legal definition of 'new drugs,' and therefore are not subject to premarket review other than satisfying the requirements of current or likely inclusion in the HPUS" (Petition at 7). Accordingly, the Petition asks that FDA agree with its conclusion that, subject to "proper" manufacturing and labeling, homeopathic drugs may be legally marketed without an approved application (Petition at 7). To effectuate this result, the Petition requests that FDA promulgate a regulation using the text proposed in section I.A. of the Petition. This text defines "homeopathic drug" as any drug that contains a single active ingredient that:

(1) is included in or certified as pending approval for inclusion in the HPUS;
(2) is generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of homeopathic drugs, as homeopathic and safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; or

(3) at any time prior to June 25, 1938, was subject to the Food and Drugs Act of June 30, 1906, as amended, if its labeling contains the same representations concerning the conditions of its use as at such time (Petition at 2-3).

The text also defines "homeopathic drug product" as "any drug product made up of two or more homeopathic drugs, and no other active ingredients" (Petition at 3).

The proposed text further states that: "Absent a determination that any specific Homeopathic drug or any specific Homeopathic drug product is a new drug, FDA will treat all Homeopathic drugs and Homeopathic drug products as generally recognized as safe and effective for their intended use (GRAS/E), subject to compliance with provisions of this regulation addressing adulteration and misbranding, and Current Good Manufacturing Practice regulations" (Petition at 6). We note that this provision, which would provide that FDA may determine that a specific homeopathic drug or homeopathic drug product (as defined in the Petition) is a new drug, is at odds with an earlier provision in the proposed text which requests that FDA declare that all products that meet the definition of homeopathic drug product are not "new drugs" (Petition at 3). Despite this seeming inconsistency, we interpret the Petition to request that we exempt products that meet any of these criteria from the premarket approval requirements of the FD&C Act (i.e., so that they may be legally marketed without an approved application) unless FDA specifically determines otherwise with respect to a particular product.

For the reasons discussed below, FDA declines to issue a regulation that, absent an FDA determination otherwise, all homeopathic drugs and drug products (as defined in the Petition) (hereinafter referred to collectively as homeopathic drug products) are exempt from existing premarket approval requirements.

1. FDA Cannot Promulgate a Regulation That Codifies a Determination That All Homeopathic Drug Products included or pending approval for inclusion in the HPUS are GRAS/E Absent an FDA Determination Otherwise.

The proposed regulation in section I.A of the Petition defines homeopathic drugs as, in part, drugs that are included in or pending approval for inclusion in the HPUS (Petition at 2). The proposed regulation in section I.A. of the Petition further would provide both that products that meet the definition of a homeopathic drug are not new drugs (Petition at 3) and that, absent a determination that any specific homeopathic drug is a new drug, FDA will treat all such drugs as GRAS/E, subject to compliance with the adulteration and misbranding provisions articulated in the Petition and with FDA CGMP regulations (Petition at 6). Therefore, section I.A. of the Petition seeks to establish by regulation that all homeopathic drug products included in or pending inclusion in the HPUS, and that are in compliance with the identified adulteration and misbranding provisions and CGMP, are GRAS/E and absent an FDA determination otherwise, are not "new drugs."

FDA disagrees with the petitioner's views about the role of the HPUS as an official compendium. The HPUS, like the USP, is a nongovernmental, official public standards-

setting authority. The HPUS, which is published by the Homeopathic Pharmacopoeial Convention of the United States, contains monographs and other information pertaining to the manufacturing of homeopathic products. The HPUS sets some standards for the manufacture of homeopathic drug products, including dilution levels. Importantly, the HPUS monographs do not specify quantities, frequency of administration, or patient population.

The existence of a drug product monograph in an official compendium[14] does *not* reflect that the compendium has made any safety or efficacy determination under the FD&C Act or the PHS Act, nor is the HPUS or USP authorized to do so. In addition, FDA does not have authority to control which monographs the compendia publish or maintain, and thus the existence of an official monograph does not reflect FDA's agreement that the product described therein is safe and effective, nor generally recognized as such (i.e., GRAS/E). Although the existence of a drug product monograph in one of the official compendia may be relevant with regard to various requirements under the Act, only FDA has the statutory authority to determine that a product is GRAS/E and exempt from the premarket approval requirements in the FD&C Act and the PHS Act.[15] Section I.A. of the Petition seeks to confer, as a de facto matter, regulatory authority with respect to the requirements for being exempt from premarket approval upon the HPUS. Conferring such authority upon the HPUS is not authorized under the FD&C Act and therefore this request in your Petition is denied.

2. A regulation stating that (absent an FDA determination otherwise) all homeopathic drug products generally recognized as safe and effective by experts in homeopathy are GRAS/E would depart from the GRAS/E standard applicable to all drugs.

The proposed regulation in section I.A. of the Petition defines homeopathic drugs as, in part, drugs that are "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of homeopathic drugs, as homeopathic and safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" (Petition at 2-3). As noted above, the proposed regulation in section I.A. of the Petition would provide both that products that meet the definition of a homeopathic drug are not new drugs (Petition at 3) and that, absent a determination that any specific homeopathic drug is a new drug, FDA will treat all such drugs as GRAS/E, subject to compliance with the adulteration and misbranding provisions articulated in the Petition and with FDA CGMP regulations (Petition at 6). Therefore, section I.A. of the Petition seeks to establish by rule that all homeopathic drug products that are "*generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of homeopathic drugs, as*

[14] Section 201(j) of the FD&C Act defines "official compendium" as "the official United States Pharmacopeia, official Homoeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them."

[15] *See Weinberger v. Bentex Pharms., Inc*., 412 U.S. 645, 653 (1973) ("FDA has jurisdiction to decide with administrative finality … the 'new drug' status of individual drugs….")

homeopathic and safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" are GRAS/E and not new drugs (absent an FDA determination to the contrary). As such, the proposed regulation would draw a distinction between "general recognition" and "general recognition by experts in homeopathy." FDA declines to promulgate such a rule because there is no basis, under our longstanding interpretation of the FD&C Act, for a regulation that draws the requested distinction.

The FD&C Act defines "drug" as

> (A) articles recognized in the official United States Pharmacopeia, official Homoeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).[16]

Under the FD&C Act, a drug can be lawfully marketed without an approved application only if it is not a new drug, or if it falls within certain limited exceptions, including one of two narrow grandfather provisions, which are discussed in a subsequent section of this response.

Under section 201(p) of the FD&C Act, the term "new drug" means

> (1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ; *or* [emphasis added]
>
> (2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Thus, under section 201(p) of the FD&C Act, a drug is a new drug if its "composition" is such that the drug "is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" (i.e., not GRAS/E). Further, under section 201(p) of the FD&C Act, a drug that is so recognized is still a new drug if it has not been used to a material extent or for a material time under such conditions.

[16] Section 201(g) of the FD&C Act.

Accordingly, the definition of the term "new drug" includes two separate criteria, either of which is sufficient to make a product a new drug: (1) lack of general recognition of safety and effectiveness; and (2) insufficient duration or extent of use. In other words, evidence of use for a material time and to a material extent alone is insufficient to render a product not a new drug requiring approval before being marketed; the drug product must also be GRAS/E. Likewise, a GRAS/E drug that has not been used for a material time or to a material extent will be considered a new drug.[17]

The legal standard for determining whether a drug product is GRAS/E within the meaning of section 201(p) of the FD&C Act is well-established in case law and requires that a drug product satisfy three criteria.[18] First, the particular drug product must have been subjected to adequate and well-controlled clinical investigations establishing that the product is safe and effective.[19] Second, those investigations must have been published in the scientific literature so that they are available to qualified experts.[20] Third, experts must generally agree, based on those published studies, that the product is safe and effective for its intended uses.[21]

Moreover, a product's general recognition as safe and effective must be evidenced by at least the same quality and quantity of data as are necessary to support approval of an NDA or BLA.[22] FDA's regulation at 21 CFR 314.126 describes the characteristics the Agency considers in evaluating whether a clinical investigation is adequate and well-controlled for purposes of determining whether there is substantial evidence of effective for a new drug. For example, per the regulation, an adequate and well-controlled clinical investigation has at least one control group, is designed to minimize bias (usually through

[17] Although the Petition asserts that the definition of "new drug" does not include homeopathic drugs (Petition at 18), it cites no support for this proposition, nor is there any such support in the FD&C Act. The statutory definition of "new drug" does not distinguish between different types of drug products, homeopathic or otherwise.

[18] *See Bentex*, 412 U.S. at 652-653 (1973) (discussing standard); *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803-804 (2d Cir. 1980) (same).

[19] *See Bentex Pharms.,* 412 U.S. at 652-653; *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 629-630 (1973); *United States v. 50 Boxes*, 721 F. Supp. 1462, 1465-1466 (D. Mass. 1989), *aff'd,* 909 F.2d 24 (1st Cir. 1990); *United States v. 225 Cartons*, 871 F.2d 409, 413 (3d Cir. 1989); *United States v. Articles of Drug*, 826 F.2d 564 (7th Cir. 1987); *United States v. Articles of Drug*, 745 F.2d 105, 118-119 (1st Cir. 1984). *See also* 21 CFR 314.200(e)(1).

[20] *See Bentex Pharms.,* 412 U.S. at 652; *United States v. An Article of Drug Consisting of 4,680 Pails*, 725 F.2d 976, 987 (5th Cir. 1984); *Premo Pharm. Labs.,* 629 F.2d at 803; *United States v. Seven Cardboard Cases,* 716 F. Supp. 1221, 1223-1224 (E.D. Mo. 1989); *United States v. 118/100 Tablet Bottles (Margesic)*, 662 F. Supp. 511, 513 (W.D. La. 1987).

[21] *See Premo Pharm. Labs.,* 629 F.2d at 802-803; *Seven Cardboard Cases*, 716 F. Supp. at 1223; *118/100 Tablet Bottles (Margesic)*, 662 F. Supp. at 514.

[22] *See Hynson, Westcott & Dunning*, 412 U.S. at 629-630; *50 Boxes*, 721 F. Supp. at 1465-1466; *225 Cartons*, 871 F.2d at 413; *Articles of Drug*, 826 F.2d 564; *Articles of Drug*, 745 F.2d at 118-119. *See also* 21 CFR 314.200(e)(1).

random assignments of study participants to control and treatment groups and through the blinding of participants and investigators to those assignments), and includes an analysis of the results of the study that is adequate to assess the effects of the drug.[23] One of the purposes of requiring adequate and well-controlled investigations is to ensure that the drug products to be taken by patients have been shown to be effective based on accepted scientific methods.[24] Rigorously controlled clinical investigations help distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.[25]

Courts have noted that the issue in a "new drug" inquiry is not just whether a drug is safe and effective, but also whether there is *general scientific recognition* of the drug's safety and effectiveness.[26] Hence the requirement that studies used to establish that a drug is GRAS/E must be published; if the studies are not publicly available to scientists, there can be no scientific basis for general recognition.

It is also well-established that anecdotal data, such as the clinical experience of practicing physicians or a drug's long history of use, cannot be the basis for finding that the drug is GRAS/E.[27] Only substantial evidence as defined by the FD&C Act will suffice for FDA to find that a drug is not a new drug.[28] The requirement that GRAS/E status be based on the same quantity and quality of evidence that would support approval of an NDA (or a BLA) is also reflected in FDA's regulations at 21 CFR 314.200(e)(1).

Finally, because the Supreme Court has held that the word "drug" in the "new drug" definition refers to the entire finished product, including excipients, and not just to the active ingredient,[29] courts generally have not been receptive when firms seek to rely on studies of one drug product to support a claim that a similar or identical drug product is GRAS/E.[30] The case law is clear that having the same active ingredient as an approved

[23] 21 CFR 314.126.

[24] *Id.* ("The characteristics described [in this regulation] have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation.").

[25] *Id.*

[26] *United States v. Undetermined Quantities of Various Articles of Drug . . .* , 675 F.2d 994 (8th Cir. 1982); *Premo Pharm. Labs*, 629 F.2d at 803-404.

[27] *United States v. Sene X Eleemosynary Corp.*, 479 F. Supp 970, 977 (S.D. Fla. 1979). *See also Upjohn Co. v. Finch*, 422 F.2d 944, 954 (6th Cir. 1970).

[28] *See Hynson, Westcott & Dunning*, 412 U.S. at 619; *50 Boxes,* 909 F.2d at 27-28*; 225 Cartons*, 871 F.2d at 418-419; *4,680 Pails*, 725 F.2d at 987; *50 Boxes*, 721 F. Supp. at 1465-1467; *Seven Cardboard Cases,* 716 F. Supp. at 1223; *United States v. Articles of Drug. . . Hormonin*, 498 F. Supp. 424, 431-432 (D.N.J. 1980).

[29] *United States v. Generix Drug Corp*., 460 U.S. 453 (1983).

[30] *225 Cartons*, 871 F.2d at 417-418; *United States v. Atropine Sulfate*, 843 F.2d 860 (5th Cir. 1988); *Articles of Drug*, 745 F.2d. 105 at 117-118; *Seven Cardboard Cases,* 716 F. Supp. at 1224-1225. A few courts that have faced most directly the issue of the applicability of studies of another drug to the drug at issue have suggested that they might permit use of those studies if there was evidence that the drug at issue

or otherwise safe and effective drug product does not establish that a drug product is GRAS/E; therefore, GRAS/E status cannot be conferred on one drug product because it has the same active ingredient as another drug product that is GRAS/E. In short, GRAS/E status is not, and cannot be, established by similarity to another drug product.[31] To establish that a drug product is GRAS/E, it must independently be shown to be safe and effective in adequate and well-controlled clinical investigations.

The Petition requests that FDA promulgate a rule under which GRAS/E status for a homeopathic drug product would be determined based on (among other applicable criteria) the "general recognition" of its safety and efficacy for its labeled indication(s), specifically by *experts in homeopathy*. Such a rule would appear to be predicated on the notion that determining the GRAS/E status of a homeopathic drug product warrants a variation from the "general recognition" standard applicable to GRAS/E determinations for drugs generally.

Congress has in certain instances treated homeopathic drug products differently than other drugs, notably in terms of compliance with the HPUS under sections 501(b) and 502(g) of the FD&C Act, with regard to adulteration and misbranding, respectively. Generally speaking, however, homeopathic drug products are treated the same as other drug products under the FD&C Act. Indeed, as noted above, the term "drug" as defined under section 201(g) of the FD&C Act includes articles recognized in the official HPUS or any supplement to it. Because homeopathic drug products are "drugs" under the Act, they are subject to the same statutory requirements as other drug products; nothing in the FD&C Act exempts homeopathic drug products from any of the requirements related to approval, adulteration, or misbranding. Significantly, in enacting the 1962 Kefauver-Harris amendments[32] to the FD&C Act, which required that manufacturers demonstrate the effectiveness of drug products as a condition of FDA approval, Congress made no distinction between allopathic and homeopathic drug products in that regard. Thus, the standards under the FD&C Act with respect to determining safety and efficacy (as described above) apply to all drug products, regardless of whether they are homeopathic or allopathic in nature. Moreover, inclusion in the HPUS does not suffice to demonstrate safety and effectiveness for purposes of FDA approval or a GRAS/E determination, as explained above. Consequently, there is no basis under the FD&C Act for applying a different GRAS/E standard with respect to homeopathic drug products.

---

was bioequivalent to the studied drug. *See 225 Cartons*, 871 F.2d at 417-418; *United States v. Undetermined Quantities of Article of Drug,* 709 F. Supp. 511 (D.N.J. 1987). To date, no court has actually found a drug to be GRAS/E based on adequate and well-controlled studies of another drug and evidence of bioequivalence.

[31] Likewise, passage of the Hatch-Waxman Amendments to the FD&C Act in 1984 provides evidence of congressional intent to subject drugs that share very similar characteristics to the application requirement. Under the Hatch-Waxman Amendments, drugs that are bioequivalent to drugs with approved NDAs still need approved ANDAs. This requirement enables FDA to evaluate active ingredients, inactive ingredients, labeling, chemical characteristics, manufacturing, controls, and other factors, in addition to bioequivalence, that combine to determine the safety and effectiveness of a finished drug product.

[32] Public Law 87-781 (Oct. 10, 1962).

The regulation proposed by the Petition would deviate from the statutory GRAS/E standard by qualifying the concept of "general recognition," such that GRAS/E determinations for homeopathic drug products would be made by "experts qualified by scientific training and experience to evaluate the safety and effectiveness of homeopathic drugs." Such conditioning of GRAS/E determinations based on expertise specifically in homeopathy would represent a significant departure from the GRAS/E standard under the FD&C Act, because for purposes of determining safety and efficacy, the Act treats homeopathic drug products the same as any other drug product. Such a departure would also be antithetical to the notion of *general* recognition under the statute.

Ultimately, the evaluation of whether a drug is a "new drug" as defined by section 201(p) of the FD&C Act is strictly a scientific determination based on the evaluation by "experts qualified by scientific training and experience…" of any published study in the scientific literature of adequate and well-controlled clinical investigations establishing that a specific product is safe and effective. The GRAS/E standard does not transform based on the medical specialty the drug product is intended for (e.g., oncology, gastroenterology, neurology, etc.) or whether it is considered part of the practice of homeopathy or any alternative medical practice (e.g., Ayurveda, Traditional Chinese Medicine, naturopathy, etc.). In other words, the scientific determination of whether a drug product is a "new drug" is the same for all drug products.

In addition, the Agency views the relevant expertise in determining whether a drug is GRAS/E for its labeled uses as hinging on an understanding of the disease state the drug is intended to address, rather than on a particular theory of medical practice. By inserting the condition that the experts qualified to make GRAS/E determinations with respect to homeopathic drug products are those "qualified by scientific training and experience to evaluate the safety and effectiveness of *homeopathic* drugs," the Petition appears intended to exclude those experts who do not have homeopathic training, even if they have specialized training and experience in the medical conditions for which a particular drug is indicated, e.g., oncologists, endocrinologists, dermatologists, or other relevant clinical specialties. If this is indeed the intent of the Petitioner, such a result would again be antithetical to the notion of *general* recognition under the statute.

In sum, the Petition seeks to establish that all homeopathic drug products that are generally recognized as safe and effective by experts in homeopathy are not new drugs. Such a rule would be inconsistent with FDA's longstanding interpretation of our statutory authority, because it would establish a separate standard for GRAS/E determinations under section 201(p) of the FD&C Act, applicable only to homeopathic drug products. Under the statute, however, the "new drug" determination is the same for all drugs. As the discussion above makes clear, each individual finished product would need to meet the same criteria for demonstrating that it is GRAS/E, as evidenced by at least the same quality and quantity of data as are necessary to support approval of an NDA or BLA.

3. FDA declines to promulgate a regulation that codifies a

determination that all homeopathic drug products entitled to "grandfathered status" are GRAS/E and Therefore Do Not Require an Approved Application to Be Legally Marketed.

The proposed regulation in section I.A. of the Petition defines homeopathic drugs as, in part, drugs that "at any time prior to June 25, 1938, [were] subject to the Food and Drugs Act of June 30, 1906, as amended, if [their] labeling contains the same representations concerning the conditions of [their] use as at such time" (Petition at 3). As previously noted, the proposed regulation in section I.A. of the Petition would provide both that products that meet the definition of a homeopathic drug are not new drugs (Petition at 3) and that, absent a determination that any specific homeopathic drug is a new drug, FDA will treat all such drugs as GRAS/E, subject to compliance with the adulteration and misbranding provisions articulated in the Petition and with FDA CGMP regulations (Petition at 6).

The provision in the Petition's proposed regulation that defines homeopathic drug product as any product that meets the definition of grandfathered under the FD&C Act does not itself contain any link to homeopathy and therefore would encompass within the definition of a homeopathic drug product *all* products that meet the grandfather requirements, regardless of whether they are homeopathic. We decline to grant the Petition's request that we find that all products that meet the grandfather requirements are homeopathic drug products. Furthermore, if a product is grandfathered, by definition it is not a new drug and is not subject to the premarket approval requirements in the FD&C Act. Therefore, we also deny the Petition's request to have the Agency issue a regulation that would permit the marketing of a homeopathic drug product that meets the grandfather definition without an approved application, because such a regulation would be unnecessary. Any homeopathic drug product that meets the grandfather definition would already be excluded from the definition of "new drug" and therefore would not need to be GRAS/E in order to be legally marketed without an approved application.[33]

Although we are denying your Petition's request that the Agency issue a regulation that would permit the marketing of a homeopathic drug product that meets the grandfather definition without an approved application, we note that any decision that a specific product is grandfathered is a fact-specific inquiry. In 1938, Congress enacted the FD&C Act, under which manufacturers of "new drugs" were required to obtain premarket approval by submitting reports of safety investigations and proposed drug labeling to FDA for review. In 1962, Congress amended the FD&C Act to require manufacturers of "new drugs" to submit to FDA additional evidence, including adequate and well-controlled clinical investigations, establishing that their drugs are not only safe but also

[33] In seeking a regulation providing that any product that meets the definition of grandfathered is also GRAS/E (unless the Agency makes a specific determination otherwise), the Petition appears to conflate the statutory standard for determining that a product is "grandfathered" and the statutory standard for determining that a product is GRAS/E. The "grandfather" provision does not rely on, nor does it lead to, a conclusion that such a product is GRAS/E. The two statutory standards for exclusion from the definition of "new drug" are distinct and thus the requested regulation is inconsistent with the FD&C Act.

effective under "the conditions of use prescribed, recommended, or suggested in their labeling."[34]

In the 1938 law, Congress exempted drugs that met the requirements of a narrow grandfather clause from certain provisions of the FD&C Act. The 1938 grandfather clause, which is codified at section 201(p)(1) of the FD&C Act, states that a "new drug" is:

> (1) Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act [on June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use . . . .

Thus, under the 1938 grandfather clause, if a drug was marketed under the Federal Food and Drugs Act of 1906 (the 1906 Act) prior to the enactment of the FD&C Act in 1938, and the drug's labeling contained the same representations concerning the conditions of its use as before the enactment of the FD&C Act in 1938, the drug is not a new drug.[35] If it is not a new drug, it is not subject to the new drug provisions of the FD&C Act, such as the new drug application provisions found in section 505 of the FD&C Act.

The term *drug*, as it is used in the "new drug" definition in section 201(p) of the FD&C Act, refers not only to the active ingredients of a drug product but to the entire finished product, including all inactive ingredients.[36] To support a contention that a drug product is exempt from the new drug definition under the 1938 grandfather clause, the sponsor must provide documentation, including but not limited to pre-1938 labeling, to

---

[34] Pub. L. 75-717, 52 Stat 1040.

[35] When Congress amended the FD&C Act in 1962, it added a second grandfather clause. The 1962 grandfather clause, which is not codified, provides that:

> In the case of any drug which, on the day immediately preceding the enactment date [on October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by [21 U.S.C. § 321(p)] of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to [21 U.S.C. § 321(p)] made by this Act shall not apply to such drug when intended solely for use under the conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Pub. L. 87-781, section 107(c)(4), 76 Stat. 780, 789. In *United States v. Allan Drug Corp.*, 357 F.2d 713, 718 (10th Cir. 1966), *cert. denied*, 385 U.S. 899 (1966), the court stated that "[w]hile the exempting language of the [1938 grandfather clause] and the [1962 grandfather clause] is verbally different, they are undoubtedly intended to mean the same thing." *Id.*

[36] *See Generix Drug Corp.*, 460 U.S. at 454, 460 (1983) (rejecting the contention "that the term 'drug' means only the active ingredient in a product" and holding that "drug" refers "to the entire product").

demonstrate that the product meets all of the criteria for "grandfather" status, including that the product as marketed today has the same formulation, strength, dosage form, route of administration, indication(s), intended patient population(s), and other conditions of use as the marketed finished drug product that was introduced into interstate commerce in the United States between January 1, 1907, and June 25, 1938.

For example, 21 CFR 314.200(e)(2) states that to support a claim of "grandfather" status, the sponsor must submit, among other things:

- "[a] copy of each pertinent document or record to establish the exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug"
- "[a] statement whether such formulation has at any subsequent time been changed in any manner … [and, if not] a copy of representative documents or records showing the formula at representative points in time"
- "[a] copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed"
- "[a] statement whether such labeling has at any subsequent time been discontinued or changed in any manner … [and, if not] a copy of representative documents or records showing labeling at representative points in time"
- "[a] copy of each pertinent document or record to establish the exact date the drug was initially marketed"
- "[a] statement whether such marketing has at any subsequent time been discontinued … [and, if so] the exact date of each such discontinuance …, together with a copy of each pertinent document or record to establish each such date"

As the foregoing discussion shows, the determination of whether a drug product is or is not a new drug under the 1938 grandfather clause of the FD&C Act is a fact-intensive determination of whether a specific drug product is the same drug product as was marketed between January 1, 1907, and June 25, 1938.[37]

B. Request that FDA recognize as safe and effective homeopathic drugs that are included or pending inclusion in the HPUS

The Petition requests that FDA formally recognize as safe and effective homeopathic drugs that are properly manufactured and labeled and listed in, or formally pending approval for listing in, the HPUS (Petition at 35). To the extent this is a request that FDA recognize homeopathic drug products that are listed or pending inclusion in the HPUS as GRAS/E, this request is denied for the reasons explained above in section

[37] *See also USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 663 (1973).

II.A.1. To the extent this is not a request that FDA recognize such products as GRAS/E, but rather a request that FDA recognize such products as safe and effective solely by virtue of their being included or pending inclusion in the HPUS, we also deny this request. As explained above, FDA disagrees with the Petition's views about the role of the HPUS as an official compendium. While the HPUS, like the USP, is a nongovernmental, official public standards-setting authority, the existence of a drug product monograph in an official compendium does not reflect that the compendium has made any safety or effectiveness determination under the FD&C Act or the PHS Act. Safety and effectiveness determinations other than GRAS/E determinations are made in the context of the review of an application under section 505 of the FD&C Act or section 351 of the PHS Act.

C. Request that FDA prohibit any drug product not included or pending inclusion in the HPUS from using the term "homeopathic"

The Petition requests that FDA prohibit any product not listed or formally pending inclusion in the HPUS from using the term "homeopathic" in its labeling or otherwise stating or implying that the product is homeopathic (Petition at 35).

The FD&C Act does not define "homeopathic drug" or "homeopathic drug product," nor does it specify that only drugs or ingredients listed in the HPUS are homeopathic. We note that the statute similarly does not limit the definition of "drugs" to those products or ingredients that are listed in the USP or National Formulary. A product may be a drug for purposes of FDA regulation regardless of whether it is included in one of the official compendia if, for example, it is an article (other than food) "intended to affect the structure or any function of the body of man or other animals."[38]

In the final guidance we define "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 [HPUS]". However, FDA's definition in the guidance for purposes of articulating our enforcement policy does not indicate an Agency intent, or signal an Agency obligation, to preclude use of the term "homeopathic" in other circumstances, for example in product labeling. The definition in the final guidance is merely intended to aid in describing the Agency's approach to enforcement with respect to homeopathic drug products.

We note that, based on your petition, the premise of this argument appears to be that products listed or pending inclusion in the HPUS are necessarily safer than those that are not. As discussed above, however, no marketed homeopathic drug products have been approved by FDA, nor has the Agency determined that any homeopathic drug products are GRAS/E. The status of being listed or pending listing in the HPUS does not remove the public health concern associated with the marketing of unapproved new drugs. Therefore, we deny this request.

[38] Section 201(g)(1) of the FD&C Act (21 U.S.C. § 321(g))

D. Request that FDA ensure that any drug product in the HPUS is manufactured in accordance with the determinations of the HPUS and CGMP requirements

The Petition requests that FDA ensure that any drug product listed in, or formally pending approval for listing in, the HPUS is manufactured "in accordance with the determinations of the HPUS" and with CGMP requirements (Petition at 35).

Under the FD&C Act, a homeopathic drug product is deemed to be adulterated if it does not comply with HPUS standards of quality, strength, and purity, or does not meet CGMP requirements.[39] In addition, a homeopathic drug product is deemed to be misbranded if it does not comply with applicable HPUS requirements for packaging and labeling.[40] All drug manufacturers, including homeopathic drug manufacturers, are subject to inspection by FDA to monitor drug product quality.[41]

We note that a homeopathic drug product may be adulterated or misbranded under the FD&C Act for reasons other than a lack of compliance with HPUS standards and CGMP requirements. Nevertheless, we interpret the Petition to be a request for the Agency to initiate enforcement action or a related regulatory activity. Decisions with respect to such matters are generally made on a case-by-case basis and are within the discretion of the Agency. Requests for the Agency to initiate enforcement action and related regulatory activity are not within the scope of FDA's citizen petition procedures (see § 10.30(k) (21 CFR 10.30(k)). Therefore, your Petition is denied.

E. Request that FDA's risk-based policy be applied with generally accepted standards and procedures of risk assessment

The Petition requests that if the FDA applies a risk-based policy to homeopathic drug products and drug products labeled as "homeopathic," the Agency ensure that such risk-based policy is formulated and applied with "generally accepted risk analysis standards" (Petition at 29, 35, Appendix 3). The Petition states that an appropriate risk-based policy would apply not to homeopathic drug products specifically, but to all products regulated by FDA, including homeopathic drug products (Petition at 29), and that homeopathic drug products should be evaluated in relation to the risks presented by other regulated products (Petition at 6). Such a policy, the Petition argues, "would demonstrate that homeopathic drugs and drug products fall into the lowest area of safety concern for all FDA regulated products" (Petition at 29.)

FDA disagrees with the assertion that the proposed risk-based policy is appropriate because homeopathic drugs are "inherently safe" (Petition at 35). As explained above, the safety of homeopathic drug products (as with all drug products) depends upon many

[39] Sections 501(a)(2)(B) and 501(b) of the FD&C Act.

[40] Section 502(g) of the FD&C Act.

[41] See section 704(a)(1) of the FD&C Act.

factors, including the manufacturing quality and the identity and amount of the "active" ingredient(s). No homeopathic drug products have been reviewed and approved by FDA for safety or efficacy; particularly given the breadth and variety of homeopathic drug products, the Agency has no basis to conclude that, as a class, they belong in a lower category of risk than other products. Therefore, this request is denied.

The Agency does not have a single statement of enforcement policy that covers all product areas, nor would such a broad statement of policy be appropriate, as it would not take into account the numerous specific considerations for each product area. However, regardless of the product area, FDA generally applies a risk-based enforcement strategy. When evaluating whether to take enforcement or other regulatory action regarding the marketing of unapproved new drugs, the agency takes into account many factors, which can include the product's intended use(s), dosage form, frequency of use, manufacturing quality, intended patient population, reported adverse events, quantity and combination of ingredients, and firm regulatory history, among others. [42]

The final guidance describes the categories of homeopathic drug products that FDA generally will consider to be higher risk and explicitly recognizes that many homeopathic drug products will fall outside the categories of products FDA intends to prioritize for enforcement.

F. Request that FDA hold a public hearing to consider the contents of this petition

The Petition requests that, if the Agency fails to grant the Petition, it hold a public hearing in accordance with the procedures of the Administrative Procedure Act (APA) to consider the contents of the Petition (Petition at 36).

As noted above, FDA held a two-day public hearing in April 2015 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.[43] FDA sought broad

[42] *See* 86 FR 28605 (May 27, 2021).

[43] The Petition makes a number of assertions regarding FDA's compliance with the APA (Petition at pp. 22-23). In particular, the Petition states that FDA announced its intention to promulgate a rule in 2015 but failed to complete that process. The Petition states that "in 2015, FDA published a document in the Federal Register entitled "Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century; Public Hearing: A Proposed Rule by the Food and Drug Administration" (Petition at 22). However, as can be seen in the Federal Register Notice cited by the Petition (footnote 54), this is not the title of the notice. The notice is titled, "Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century; Public Hearing." Under the heading of "Action," the notice states: "Notice of public hearing; request for comments." The notice does not reference a proposed rule or the intent to promulgate one. The Petition also states, erroneously, that the Agency held "an informal public meeting rather than following the Administrative Procedure Act and holding a formal public hearing identified in its announcement" (Petition at 8). The 2015 public hearing was convened by FDA pursuant to 21 CFR part 15 and fully complied with the requirements in those regulations.

public input on its enforcement policies related to homeopathic drug products in an effort to better promote and protect the public health. The docket for this hearing remained open until November 2016, and the Agency received more than 9,000 comments from a wide variety of stakeholders. As a result of the Agency's evaluation, including consideration of the information obtained as a result of the public hearing, FDA issued the draft guidance in December 2017 for public comment. The Agency received and thoroughly considered more than 4,500 comments to that docket. FDA then issued a revised draft guidance in October 2019, to enable additional public input and received and reviewed more than 50,000 additional comments.

Given the broad, extensive feedback the Agency has already received from relevant stakeholders, as well as the thorough consideration the Agency has brought to these issues, FDA finds that an additional public hearing is not necessary at this time. This request is therefore denied.

III. CONCLUSION

For the reasons stated above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.12.06 09:47:37 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research