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Dockets Management Staff (HFA-305)
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U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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RE: Docket No. FDA–2017–D–6580 for "Drug Products Labeled as Homeopathic; Draft Guidance for Food and Drug Administration Staff and Industry; Availability" (Publication Date: December 20, 2017)

Dear Sir or Madam:

The Natural Products Association (NPA) is submitting this letter as general comment to docket FDA–2017–D–6580 (Docket Name: Drug Products Labeled as Homeopathic; Draft Guidance). The NPA was founded in 1936 to promote and protect the unique values and shared interests of retailers and suppliers of natural nutritional foods and natural products, including over-the-counter (OTC) and prescription homeopathic drugs. The NPA is a non-profit 501(c)(6) association whose mission is to advocate for the rights of consumers to have access to products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these products. We are the oldest and largest trade association in the natural products industry representing over 1,900 members accounting for almost 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, homeopathic products, and health/beauty aids. Many of our members manufacture or sell

homeopathic products, and therefore NPA has an interest to submit comments on this topic. Thank you for the opportunity to comment.

In the Federal Register on March 27, 2015 (80 FR 16327), the Food and Drug Administration (FDA) published their notification of a public meeting, titled "Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century," and requested comments on this topic. The public meeting was held on Apr. 20 and 21, 2015, and NPA submitted comments responsive to FDA's questions directed at industry. FDA sought alternative strategies and clarity to the current application of enforcement discretion on homeopathic drugs, policies in the homeopathic Compliance Policy Guide (CPG 7132.15/CPG 400.400), how current homeopathic companies evaluate their products, how other countries regulate homeopathic products, whether labeling for homeopathics is adequate at present, and what information do firms use to help them make decisions on marketing their homeopathic drug.

This Federal Register notice announces the availability of a draft guidance for FDA staff and industry describing how FDA intends to prioritize enforcement and regulatory action with regard to drug products, including biological products, labeled as homeopathic and marketed in the United States without the required FDA approval. FDA stated that it also plans to withdraw Compliance Policy Guide (CPG) 400.400, "Conditions Under Which Homeopathic Drugs May be Marketed", issued on May 31, 1988. FDA wrote that it sought broad input on its enforcement policies related to drug products labeled as homeopathic in an effort to better promote and protect the public health. In the Federal Register, FDA wrote,

> "As a result of the Agency's evaluation, including consideration of the public input received on this issue, FDA has determined that it is in the best interest of public health to issue a new guidance that applies a risk-based enforcement approach to drug products labeled as homeopathic and marketed in the United States without the required FDA approval, consistent with FDA's risk-based regulatory approaches generally. The Agency generally intends to apply a risk-based

> enforcement approach to the manufacturing, distribution, and marketing of drug products labeled as homeopathic, as described in the draft guidance, when finalized."

NPA will comment on this strategy to move to a risk-based enforcement approach and eliminate CPG 400.400 later on.

Background on Homeopathic Products

Homeopathy, an area of complementary and alternative medicine (CAM), was developed in 1796 by Samuel Hahnemann, a trained physician. Dr. Hahnemann disputed many medical practices of his day, including bloodletting, because they often caused more harm and suffering, a clear antithesis of the Hippocratic oath of his day to do no harm. After treating malaria with the quinine-containing bark from the Peruvian cinchona tree, he noticed the bark itself induced minor malaria-like symptoms in himself or any healthy individual. This observation led to his theory which forms the basis of homeopathy today: "that which can produce a set of symptoms in a healthy individual, can treat a sick individual who is manifesting a similar set of symptoms" or more simply, "like cures like".

The Federal Food Drug and Cosmetic Act (FD&C Act) is the primary law governing the regulation of prescription and non-prescription substances used to treat illness. This law identifies substances acceptable for sale as medicines such as those listed in official compendia. The inclusion of homeopathic remedies as accepted drugs in the original legislation was largely through the efforts of Senator Royal Copeland, a physician, homeopath and architect of the FD&C Act.

Regulation of Homeopathic Products in the United States

Since 1938, Congress declared that homeopathic remedies would be regulated by FDA in the same manner as non-prescription, over-the-counter (OTC) drugs.[1] Because of their long history of use and dilute ingredients, homeopathics have always been able to be purchased without a physician's prescription. While conventional prescription drugs and new OTC drugs must undergo testing and approval (drug review) by the FDA for safety and effectiveness before they can be sold, the agency charged with protecting the public health for foods, drugs, and devices, has not applied these requirements to homeopathic remedies. Most homeopathic remedies have been made available and sold as OTC products, though some homeopathic drugs might require a prescription depending on the way they are marketed to the consumer. If a symptom is expected to be easily recognized by a lay person and self-limiting or not life-threatening, then a homeopathic remedy for such a symptom can be sold without a prescription.[2] In other words, remedies intended for use in conditions that are serious, not self-limiting, and not easily diagnosed by lay persons still require a prescription as they always have, and these drugs are heavily scrutinized by FDA.

In the early 1970s, FDA officials recognized that homeopathic preparations were attracting a greater share of OTC sales among lay persons for health food stores, but FDA took few actions against OTC homeopathic drugs. FDA did take action on a Canadian firm because the combination of ingredients was not recognized in any official homeopathic compendium, a fundamental principle of homeopathy. The U.S. District Court for the District of Nevada would

[1] § 201(g)(1) [21 U.S.C. § 321(g)(1)] The term "drug" means (A) articles recognized in the official United States Pharmacopeia, official Homeopathic 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 articles specified in clause (A), (B), or (C).
[2] Remedies intended for use in conditions that could be serious, not self-limiting, and not easily diagnosed by laypeople require a prescription. If products are found to be offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, FDA will determine them to be misbranded drugs which have violated a prohibited act. FDA typically cites §502(f)(1) [21 U.S.C. § 352(f)(1)] and 301(a) [21 U.S.C. § 331(a)] for such products.

later uphold the agency's detention policy of misbranded homeopathic drugs.[3] In 1972, FDA initiated formal rulemaking procedures for OTC drugs to determine which are generally recognized among qualified experts as safe and effective and not misbranded under the prescribed, recommended, or suggested conditions of use.[4] FDA chose to exclude homeopathic drugs from its OTC drug review. Due to shifting priorities, FDA chose to defer the review of homeopathics under the OTC drug review and stated FDA would review them as a separate category in the future.[5] Up until this latest FDA inquiry, FDA has chosen never to review homeopathics for safety and efficacy.

While there are no FDA monographs for homeopathics, the FD&C Act does recognize the Homeopathic Pharmacopoeia of the United States (HPUS), along with the United States Pharmacopeia (USP), and National Formulary (NF) as official compendiums.[6] While HPUS is produced by a non-governmental organization (NG, the Homeopathic Pharmacopoeia Convention of the United States (HPCUS), it has been in publication since its inception in 1897.[7] The HPUS has served as a valuable resource to FDA on nomenclature, quality, and labeling for over a century. While nothing in the FD&C Act exempts homeopathics from the requirements for approval of new drugs,[8] adulteration, and misbranding, there are well over 1,300 officially monographed ingredients in the HPUS in existence today, and the standards reflect the

[3] Mesery v. United States, 447 F. Supp. 548 (D. Nev. 1977).
[4] 37 FR 9464, May 11, 1972.
[5] 37 FR 9464 at 9466.
[6] § 201(j) [21 U.S.C. 321(j)] The term "official compendium" means the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official national Formulary, or any supplement to any of them.
[7] Committee on Pharmacy of the American Institute of Homeopathy. 1897. Homeopathic Pharmacopoeia of the United States, First Edition. Otis Clapp, Boston.
[8] § 201(p) [21 U.S.C. 321(p)] A "new drug" is defined, in part, as any drug that 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 condition prescribed, recommended, or suggested in the labeling thereof.

nomenclature, quality and labeling of these homeopathic products as per the FD&C Act.[9,10] There have been over 500 new ingredient monographs added by HPCUS over the past 10 years.

During the late 70s and early 80s, growth in the number of manufacturers and the market for OTC homeopathic drugs pushed FDA to reassess their hands-off position on homeopathic drugs. FDA surveyed the marketplace in 1981 to find a thriving industry of self-help homeopathic products and an increasing number of imports from overseas. These changes in the homeopathic marketplace reignited discussions throughout the 80s concerning agency policy on homeopathic drug regulations. On June 9, 1988, FDA announced[11] a new CPG for homeopathic drugs.[12] The new CPG provided warning shots to firms offering homeopathic drugs for conditions "significantly beyond the recognized practice of homeopathy" and suggested they would be subject to prosecution for health fraud. The new regulatory framework in the CPG strengthened the definition of a homeopathic drug, set forth guidelines for prescription and nonprescription drugs, and provided clear guidelines for packaging, labeling, indications for use, and homeopathic names. Since remedies are required to meet certain regulatory standards for strength, quality, purity, and packaging, FDA required that all homeopathic remedies list the indications for their use on the label starting in 1988. FDA also required the listing of all ingredients and disclose the

[9] § 501(b) [21 U.S.C. 351(b)] A drug or device shall be deemed to be adulterated — (b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium … Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States it shall be subject to the requirements of the United States Pharmacopeia unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States and not to those of the United States Pharmacopeia.

[10] § 502(g) [21 U.S.C. 352(g)] A drug or device shall be deemed to be misbranded — (g) If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein. … Whenever a drug is recognized in both the United States Pharmacopeia and the Homeopathic Pharmacopeia of the United States, it shall be subject to the requirements of the United States Pharmacopeia with respect to packaging, and labeling unless it is labeled and offered for sale as a homeopathic drug, in which case it shall be subject to the provisions of the Homeopathic Pharmacopeia of the United States, and not to those of the United States Pharmacopeia …

[11] 53 FR 21728, June 9, 1988

[12] "For use under supervision of a licensed practitioner experienced in the use and administration of homeopathic drugs and familiar with indications, effects, dosages, methods, and frequency of duration of such drugs." FDA Compliance Policy Guide, Sec. 400.400, "Conditions Under Which Homeopathic Drugs May Be Marketed," CPG 7132.15.

dilutions. The key element in the CPG was that for homeopathic drugs to be sold OTC, they have to be marketed for a self-limiting condition which does not require medical diagnosis or monitoring and was non-toxic. Additionally, the homeopathic needs to be fully labeled with at least one indication for use.

Guidelines for homeopathic remedies can be found in the HPUS. The HPUS also includes provisions for testing new remedies and verifying their clinical effectiveness. Remedies on the market before 1962 were grandfathered into the HPUS based on safety of historical use rather than other evidence (e.g. clinical trials) of safety and effectiveness; however, FDA asked for the HPUS to be "cleaned up". This prompted the first installment of the new edition of the HPUS, which became the Homeopathic Pharmacopeia Revision Service (HPRS). As a result of the CPG, numerous remedies that were once sold as OTC products were moved to prescription status starting on the June 9, 1990 effective date. Any drug included in the HPRS would be "official and those not included in the HPRS would be "non-official". Therefore, any official drug could be sold without any further documentation provided from the manufacturer. Manufacturers of non-official drugs are required to submit a proving or sufficient clinical data for the FDA to make a determination as to whether the drug was in fact homeopathic (FDA pre-approval). Therefore, homeopathic drugs have an active pre-approval regulatory structure in place.

While FDA takes the position that a homeopathic product's compliance with the requirements of the HPUS, USP, or NF does not establish that it has been shown by appropriate means to be safe, effective, and not misbranded for its intended use, it is necessary to understand the eligibility criteria for an ingredient to be included as a monograph in the HPUS.

- The HPCUS must determine that the homeopathic is safe and effective.
- The homeopathic must be prepared according to the specifications of the General Pharmacy and relevant sections of the Homeopathic Pharmacopeia of the United States.
- The submitted documentation must be in an approved format as set forth in the relevant sections of the Homeopathic Pharmacopeia of the United States.

Homeopathic ingredients must also meet one of the following four criteria.

- The therapeutic use of the drug is established through is established through published documentation that the substance was in use prior to 1962.[13]
- The therapeutic use of a new and non-official homeopathic drug is established by a homeopathic drug proving and clinical verification acceptable to the HPCUS. During the period of clinical verification the drug will be accepted for provisional review and should be available on a monitored basis.
- The therapeutic use of the homeopathic drug is established by 1) data gathered from clinical experience encompassing the symptom picture, pre- and post-treatment, including subjective and any available objective symptoms or 2) data documented in the medical literature (all sources of medical literature may be considered on a case by case basis) subjected to further verification (statistical and/or other forms of verification).

Homeopathic Drugs are Already Regulated

Many homeopathic drugs are manufactured and distributed without FDA prior approval under FDA enforcement policy guide Sec. 400.400 set forth in "Conditions Under Which Homeopathic Drugs May Be Marketed (CPG 7132.15)". As its title suggests, the CPG identifies specific conditions under which homeopathic drugs may ordinarily be marketed; thus, homeopathics must meet the conditions set forth in the CPG to remain within the enforcement discretion safe harbor of the CPG. FDA has regulatory authority over homeopathic drugs which stray from the law, and they have exercised that enforcement discretion.

[13] The Kefauver amendments to the FD&C Act were in response to the thalidomide scandal. The criterion of clinical use prior to 1962 was used to grandfather many drugs in the 1970s and 1980s. The HPCUS promulgated guidelines for approving new homeopathic drugs. The Kefauver-Harris amendments generated questions about the extent to which homeopathic drugs should be required to conform to the law's new efficacy provisions in Pub. L. No. 87-781, 76 Stat. 780 (1962)(21 U.S.C. § 321 et seq).

Homeopathic drugs are subject to the same regulatory requirements as other drugs; nothing in the Act exempts homeopathic drugs from any of the requirements related to adulteration, labeling, misbranding, or approval. FDA has the tools to remove harmful products from store shelves. It can take administrative actions like warning letters to aggressive enforcement actions including seizures and injunctions against a firm introducing misbranded or adulterated homeopathics into interstate commerce. FDA can enlist states with embargo authorities. Claims that go beyond those permitted for conditions that are amenable to self-diagnosis and treatment by individuals who are not medical practitioners, FDA can charge them as unapproved new drugs[14] and for committing a prohibited act through introduction or delivery of a misbranded or adulterated product into interstate commerce.[15] FTC can go after homeopathic products if it finds that the claims are not substantiated with competent and reliable scientific evidence, which usually means they fail to demonstrate efficacy with a placebo-controlled, randomized, clinical trial (RCT). FDA and FTC have sent warning letters to firms.[16,17]

Joint Federal Trade Commission (FTC)/FDA letters to firms marketing homeopathic products containing human chorionic gonadotropin (HCG) for weight loss demonstrate active use of federal authorities and oversight for unlawful advertisements and ingredients.[18] In those letters, FTC and FDA state that the firms do not have competent and reliable scientific evidence to support their claims for weight loss. FTC is very aggressive on enforcing the scientific standard of "competent and reliable" for dietary supplements, homeopathics, and other commodities regulated by FDA. Homeopathic products labeled to contain HCG as the active ingredient are not considered homeopathic drugs because HCG is not listed in any recognized *materia medica* containing information on the preparation of homeopathic medicines.

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[14] § 502(f)(1) [21 U.S.C. § 352(f)(1)]
[15] § 301(a) [21 U.S.C. § 331(a)]
[16] http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm281528.htm
[17] https://www.ftc.gov/news-events/press-releases/2014/12/federal-trade-commission-continues-crackdown-fad-weight-loss
[18] http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?qryStr=homeopathic+hcg&sortColumn=&Go=Go&webSearch=true

NPA believes that the current enforcement policies under the FDA's CPG are appropriate and sufficient to protect consumers, protect public health, and provide for access to a wide array of ingredients for self-limiting, non-life threatening symptoms and ailments that are amenable to self-diagnosis and self-treatment. The FD&C Act provides FDA with the current tools required to support administrative and official agency enforcement actions. FDA has the tools to take immediate corrective action to remove dangerous products from store shelves. Effective enforcement has taken place already through application of FDA's CPG for homeopathic drugs and enforcement discretion. NPA supports future enforcement of misbranded/adulterated homeopathic drugs in accordance with the current CPG and removal of products found to be harmful to consumers. NPA also supports the existing post-market surveillance of products and ingredients in place at FDA through the Center for Drug Evaluation and Research (CDER) Adverse Event Reporting System (AERS) to monitor adverse events for a toxicological signal. If FDA regulates homeopathics with a pre-approval system, which has occurred in other countries, the premarket authorization process here will be overwhelming. The United States will experience 3-year backlogs for ingredients and products which have a safe track record. In turn, this will interfere with industry innovation and consumer access to those homeopathic products.

NPA requests that FDA indicate why it is making the decision to dump Section 400.400 of its current CPG in favor of a finalized guidance based on a risk-based strategy. NPA requests FDA to explain whether it is because it is has concerns over serious adverse events that have been reported to the Agency's AERS. Has FDA performed an analysis to show that switching from its current strategy in 400.00 to a new risk-based strategy is material? NPA requests FDA publish these critical documents before going to finalized guidance out of government transparency.

<u>Homeopathics are Adequately Labeled for Consumers</u>

NPA believes consumers and health care providers have adequate information to make informed decisions about drug products labeled as "Homeopathic." Homeopathic products sold OTC through retail stores are labeled with a clear listing of their ingredients, conditions of use,

target population, claims for intended use, directions for use, and warning statements. Label information is provided under the title heading "Drug Facts," and products have a statement of identity as a "Homeopathic" or "Homeopathic Medicine". Labeling informs consumers when it is appropriate to discontinue use and contact a health care provider. In this way, consumers are able to make informed decisions about their choices. The labeling of homeopathic OTC drugs is informative and useful for consumers to self-diagnose and self-treat their self-limiting conditions. NPA believes the majority are labeled appropriately. NPA supports enforcement against misbranded and adulterated products. NPA would like to know if FDA has possession of data on the number of products devoid of responsible labeling on homeopathic OTC products. To assume irresponsible labeling on products in the majority of cases without empirical evidence is neither scholarly nor free of bias. If FDA finds products to be misbranded or adulterated, NPA supports enforcement against these products.

NPA member companies use the homeopathic CPG 400.00 ("self-limiting disease conditions amenable to self-diagnosis") as the basis to determine if their products are appropriate for OTC sale. The majority of homeopathic OTC drug products are appropriately labeled in compliance with FDA regulations (codified regulations of the CFR) and HPUS. Branded retail products fall into OTC monograph categories, established by FDA and HPUS, if amenable to self-diagnosis and self-treatment by lay persons. NPA member companies also look to FDA's guidance and final monographs for OTC drugs when establishing conscientious indications for use.

Homeopathic Drugs are Safe

The HPUS is a living document developed by a group of physicians, pharmacists and lay persons meeting several times a year to review drug monographs and pharmacy procedures. As stated previously, the HPUS was revised with the HPRS of 1988. Today, over 400 drugs are prescription at some level of potency. For a drug to even appear in the HPRS, it needs to have sufficient clinical data or proving to demonstrate efficacy. In order to remain under OTC status in

the HPRS, the drug needs to be non-toxic and provide an OTC indication. Staunch critics of homeopathic remedies suggest these products are merely water because the active ingredients are so dilute. If we take their statements at face value, it would suggest homeopathics are about the safest product on the planet. Homeopathic medicines in high dilutions, and taken under the supervision of trained healthcare professionals, are considered safe and unlikely to cause severe adverse reaction. Some detractors of homeopathic products have said the HPRS contains over 1,300 different formulations of water. These critics mostly point to dilutions of the active ingredient as a sufficient reason for assuming lack of efficacy. Scientific evidence needs only one line of evidence to refute such an absurd assertion and hypothesis.[19] While some patients report an initial malaise after starting homeopathic remedies, homeopaths understand this to be the body's response as it restores health. The ingredients in homeopathic remedies do not interfere with conventional drugs given their dilute nature. NPA always advocates that consumers should consult their health care provider before taking any product, including homeopathic drug remedies for self-medication. NPA supports the notion that homeopathic drugs are safe. If a safety issue arises as with any commodity, FDA has the tools to remove the product or ingredient from the marketplace. Homeopathic drugs would have experienced many more enforcement action over safety if there were concerns. Either FDA has chosen to look the other direction if they possessed significant safety signals in case reports, the toxicology signals they have in their possession are not causally linked to ingestion of the homeopathic, or there are no adverse event data to warrant a concern.

Homeopathic Drugs Demonstrate Efficacy

A literature review of 104 papers demonstrating adequate quality with placebo-controlled RCTs on homeopathic drugs indicated effects over placebo warranting further study for 41%, negative evidence for 5%, and no conclusive evidence for 54% of the studies. These

[19] Frenkel M., Mishra B.M., Sen S., Yang P., Pawlus A., Vence L., Leblanc A., Cohen L., and Banerji P. (2010). Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol* 36(2): 395-403.

numbers are similar to the breakdown of evidence from an analysis of 1,016 reviews of RCTs for conventional medicines.[20] A number of scientific systematic reviews on homeopathy have evaluated the state of clinical evidence for a wide variety of clinical symptoms. Nine of 35 systematic reviews were positive for homeopathic conditions such as post-operative ileus,[21] allergies and upper respiratory tract infections,[22,23] seasonal allergic rhinitis,[24,25,26] vertigo,[27] diarrhea in pediatric populations,[28] and rheumatic ailments (e.g. those affecting the joints of the body).[29]

A number of clinical trials can be found which demonstrate a benefit for homeopathy over placebo. For example, evidence of a benefit exists for homeopathy over placebo in heavy metal

[20] El Dib RP, Atallah A.N., and Andriolo R.B. (2007) Mapping the Cochrane evidence for decision making in health care. *J Eval Clin Prac* 13: 689-692. 44 % concluded that the interventions studied were likely to be beneficial, 7% concluded the interventions were likely to be harmful, and 49% of reviews reported that the conventional medicine evidence did not support either benefit or harm. 96% of all reviews for intervention with medicine recommended further research.
[21] Barnes J, Resch K.L. and Ernst E. (1997). Homeopathy for postoperative ileus? A meta-analysis. *J Clin Gastroent* 25: 628-633.
[22] Bornhöft G., Wolf U., Ammon K. et al. (2006). Effectiveness, safety and cost-effectiveness of homeopathy in general practice – summarized health technology assessment. *Forschende Komplementärmedizin* 13(2): 19-29.
[23] Bellavite P., Ortolani R., Pontarollo F., et al. (2006). Immunology and homeopathy. 4. Clinical studies – Part 1. Evidence-based Complementary and Alternative Medicine: eCAM 3: 293-301.
[24] Wiesenauer M. and Lüdtke R. (1996). A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca. *Forschende Komplementärmedizin und Klassische Naturheilkunde* 3: 230-236.
[25] Taylor M.A., Reilly D., Llewellyn-Jones R.H., et al. (2000). Randomised controlled trials of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *Brit Med* J 321: 471-476.
[26] Bellavite P., Ortolani R., Pontarollo F., et al. (2006). Immunology and homeopathy. 4. Clinical studies – Part 2. Evidence-based Complementary and Alternative Medicine: eCAM 3: 397-409.
[27] Schneider B., Klein P., Weiser M. (2005). Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. *Arzneimittelforschung* 55: 23-29.
[28] Jacobs J., Jonas W.B., Jimenez-Perez M., and Crothers D. (2003). Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Ped Infect Dis J* 22: 229-234.
[29] Jonas W.B., Linde K., and Ramirez G. (2000). Homeopathy and rheumatic disease. *Rheum Dis Clin North Amer* 26: 117-123.

toxicity,[30,31,32] allergies,[33,34,35,36,37,38,39] pediatric diarrhea,[40,41,42,43] psoriasis,[44] infection, inflammation[45,46,47,48,49,50,51,52,53] and pain.[54] This is an abbreviated list of the various conditions

[30] Belon P., Banerjee A., Karmakar S.R., Biswas S.J., Choudhury S.C., Banerjee P., Das J.K., Pathak S., Guha B., Paul S., Bhattacharjee N. and Khuda-Bukhsh A.R. (2007). Homeopathic remedy for arsenic toxicity? Evidence-based findings from a randomized placebo-controlled double blind human trial. *Sci Tot Env* 384: 141-150.
[31] Belon P., Banerjee P., Choudhury S.C., Banerjee A., Biswas S.J., Karmakar S.R., Pathak S., Guha B., Chatterjee S., Bhattacharjee N., Das J.K. and Khuda-Bukhsh A.R. (2006). Can administration of potentized homeopathic remedy, Arsenicum album, alter antinuclear antibody (ANA) titre in people living in high-risk arsenic contaminated areas? I. A Correlation with certain hematological parameters. *Evidence-Based Comp Alt Med* 3: 99-107.
[32] Khuda-Bukhsh A.R., Pathak S., Guha B., Karmakar S.R., Das J.K., Banerjee P., Biswas S.J., Mukherjee P., Bhattacharjee N., Choudhury S.C., Banerjee A., Bhadra S., Mallick P., Chakrabarti J., and Mandal B. (2005). Can homeopathic arsenic remedy combat arsenic poisoning in humans exposed to groundwater arsenic contamination? A preliminary report on first human trial. *Evidence-Based Comp Alt Med* 2: 537-548.
[33] Naidoo P. and Pellow J. (2013). A randomized placebo-controlled pilot study of cat saliva 9cH and Histaminum 9cH in cat allergic adults. *Homeopathy* 102: 123-129.
[34] Taylor M.A., Reilly D., Llewellyn-Jones R.H., McSharry C. and Aitchison T.C. (2000). Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *Brit Med J* 321: 471-476.
[35] Aabel S., Laerum E, Dolvik S., and Djupesland P. (2000). Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the isopathic remedy Betula 30c for patients with birch pollen allergy. *Brit Homeopath J* 89: 161-168.
[36] Kim L.S., Riedlinger J.E., Baldwin C.M., Hilli L., Khalsa S.V., Messer S.A. and Waters R.F. (2005). Treatment of seasonal allergic rhinitis using homeopathic preparation of common allergens in the southwest region of the US: a randomized, controlled clinical trial. *Ann Pharmaco* 39: 617-624.
[37] Aabel S. (2001). Prophylactic and acute treatment with the homeopathic medicine Betula 30c for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. *Brit Homeopath J* 90: 73-78.
[38] Reilly D.T., Taylor M.A., McSharry C. and Aitchison T. (1986). Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model. *Lancet* 2: 881-885.
[39] Wiesenauer M., Ludtke R. (1995). The treatment of pollinosis with Galphimia glauca D4 – a randomized placebo-controlled double-blind clinical trial. *Phytomed* 2: 3-6.
[40] Jacobs J., Jimenez L.M., Gloyds S.S., Gale J.L. and Crothers D. (1994). Treatment of acute childhood diarrhea with homeopathic medicine: a randomized clinical trial in Nicaragua. *Pediatrics* 93: 719-725.
[41] Jacobs J., Jimenez L.M., Malthouse S., Chapman E., Crothers D., Masuk M. and Jonas W.B. (2000). Homeopathic treatment of acute childhood diarrhea: results from a clinical trial in Nepal. *J Alt Comp Med* 6: 131-139.
[42] Jacobs J., Jiminez L.M., Gloyds S.S., Casares F.E., Gaitan M.P. and Crothers D. (1993). Homoeopathic treatment of acute childhood diarrhea. A randomized clinical trial in Nicaragua. *Brit Homoeopath J* 82: 83-86.
[43] Jacobs J., Guthrie B.L., Montes G.A., Jacobs L.E., Mickey-Colman N., Wilson A.R. and DiGiacomo R. (2006). Homeopathic combination remedy in the treatment of acute childhood diarrhea in Honduras. *J Alt Comp Med* 12: 723-732.
[44] Bernstein S., Donsky H., Gulliver W., Hamilton D., Nobel S and Norman R. (2006). Treatment of mild to moderate psoriasis with Relieva, a Mahonia aquifolium extract – a double-blind, placebo-controlled study. *Amer J Ther* 13: 121-126.
[45] Zabolotnyi D.I., Kneis K.C., Richardson A., Rettenberger R., Heger M., Kaszkin-Bettag M. and Heger P.W. (2007). Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. *Explore* (NY) 3: 98-109.

and symptoms for which homeopathic drugs have demonstrated some effect over placebo in RCTs.

FDA's New Homeopathic Draft Guidance May Exceed What Can Be Addressed Through the Guidance Process

FDA wrote that "[a]s a result of the Agency's evaluation, including consideration of the public input received on this issue, FDA has determined that it is in the best interest of public health to issue a new guidance that applies a risk-based enforcement approach to drug products labeled as homeopathic and marketed in the United States without the required FDA approval, consistent with FDA's risk-based regulatory approaches generally. The Agency generally intends to apply a risk-based enforcement approach to the manufacturing, distribution, and marketing of drug products labeled as homeopathic, as described in the draft guidance, when finalized." The Agency also wrote that it would discard sec. 400.400 of the old CPG in favor of this guidance. This statement would seem to mark a major change in the agency's policy, especially regarding

[46] Weisenauer M., Gaus W., Bohnacker U. and Haussler S. (1989). Efficiency of homeopathic preparation combinations in sinusitis. Results of a randomized double blind study with general practitioners. *Arzneimittel Forschung* 39: 620-625.
[47] Weiser M. and Clasen B. (1994). Randomized, placebo-controlled, double-blind study of the clinical efficacy of the homeopathic Euphorbium compositum-S nasal spray in cases of chronic sinusitis. *Forschende Komplementärmedizin* 1: 251-259.
[48] Diefenbach M., Schilken J., Steiner G. and Becker H.J. (1997). Homeopathic therapy in respiratory tract diseases. Evaluation of a clinical study in 258 patients. *Zeitschrift fur Allgemeinmedizin* 73: 308-314.
[49] Oberbaum M., Yaniv I., Ben-Gal Y., Stein J., Ben-Zvi N., Freedman L.S. and Branski D. (2001). A randomized, controlled clinical trial of the homeopathic medication Traumeel S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer* 92: 684-690.
[50] Jacobsa J., Springer D.A. and Crothers D. (2001). Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. *Ped Infec Dis J* 20: 177-183.
[51] Malapane E., Solomon E.M. and Pellow J. (2014). Efficacy of a homeopathic complex on acute viral tonsillitis. *J Alt Comp Med* 20: 868-873.
[52] Ferley J.P., Zmirou D, D'Adhemar D. and Balducci F. (1989). A controlled evaluation of a homoeopathic preparation in the treatment of influenza like syndromes. *Brit J Clin Pharmacol* 27: 329-335.
[53] Papp R., Schuback G., Beck E., Burkard G., Bengel J., Lehrl S. and Belon P. (1998). Oscillococcinum® in patients with influenza-like syndromes: a placebo-controlled double-blind evaluation. *Brit Homoeopath J* 87: 69-76.
[54] Clark J. and Percivall A. (2000). A preliminary investigation into the effectiveness of the homeopathic remedy, Ruta graveolens, in the treatment of pain in plantar fasciitis. *Brit J Pod* 3: 81-85.

enforcement discretion in this area. Should this guidance be referenced by the agency in future enforcement activities, to effectively narrow the scope of a regulatory category in effect since 1972 such an event would appear to be at odds with the Administrative Procedures Act (APA), and more importantly the agency's transparency initiative. Under the APA, notice-and-comment rulemaking is also required whenever a federal agency wants to act in a way that materially changes established burdens and benefits "*by which rights or obligations have been determined, or from which legal consequences will flow*"[55], which one would believe would accurately describe any enforcement activities against products which are currently meeting all regulatory requirements necessary to be lawfully marketed as homeopathic drugs but are determined to be unapproved drugs by the agency solely on the basis of not having the new homeopathic disclaimer statement or how the product is labeled or packaged. The established legal consequences of non-compliance with the Agency's policies always included but have not been previously limited to: Warning Letters; seizure; injunction; civil penalties; and/or prosecution. Complicating matters further, while Good Guidance Practice (GGP) requirements call for the Agency's review of public comments to a draft guidance document, FDA is not required to explain or respond to any of the comments filed on the finalization of that guidance. Thus, the comments the Agency receives are merely a formality, the agency can finalize the guidance at any time and not have to provide any substantiation or justification of their position in the face of comments by interested parties. While the lawfulness of the good guidance practices is not in question, the spirit of them certainly should be put front and center. Without any insight into the Agency's rationale, such an exercise does not ring of an open, public and transparent dialogue. In addition, the Agency has previously formed a task force to develop recommendations for making useful and understandable information about FDA activities and decision making more readily available to the public in a timely manner and in a user-friendly format.[56]

As the agency is interested in transparency, then it would seem appropriate to, when the guidance is finalized, provide response to comments, and insight as to why it is rejecting or

[55] Bennett v. Spear, 520 U.S. 154, 178 (1997).
[56] https://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm (accessed February 20, 2018)

accepting comments for incorporation in the guidance. If doing such is not appropriate under the current good guidance practices then by comparison, the Agency, under notice-and-comment rulemaking, would respond to the comments filed. Providing the justification to the public why it either rejects comments or incorporates them into a final rule would seem reasonable. Such an open, public justification informs the public of FDA's rationale in rejecting and accepting comments and also reveals the Agency's reason for the guidance in the first place.

Conclusions

The FDA has decided to once again look at homeopathic regulations after more than 25 years due to their increased presence in the marketplace. Since homeopathic drugs were never addressed in 1972 when FDA established the OTC Drug Review, they are currently regulated as drugs with enforcement discretion. Although there have been some guidelines for homeopathic products, FDA has not approved any homeopathic drugs (prescription and nonprescription) due to enforcement discretion and policies set forth in FDA's homeopathic CPG. The FDA sought alternative strategies and clarity to the current policies in the CPG, how current homeopathic companies evaluate their products, and how other countries regulate homeopathic products. In the interim, FDA has decided to push forward the present guidance and discard the former sec. 400.400 of the CPG once this guidance has been finalized.

NPA supports FDA in their mission to protecting public health, while allowing consumers to have access to a wide range of homeopathics, the rights of manufacturers to sell homeopathics, and removal of unsafe homeopathic products from the marketplace. FDA has laws in place in the FD&C Act and the codified federal regulations (CFR) to enforce against misbranded and adulterated homeopathic (OTC and prescription) products. The vast majority of homeopathic products are labeled appropriately and include the appropriate statement of identity as "Homeopathic." The label information is sufficient for consumers to make informed choices within FDA's homeopathic CPG 7132.15, which allows products for self-limiting disease conditions amenable to self-diagnosis. FDA's homeopathic CPG in sec. 400.400 has held a track

record of success in the number of warning letters and enforcement actions taken over the past decade. FDA has used it to remove HCG from the marketplace because it is not listed in an official compendium. The current CPG is presently a workable platform upon which FDA can use to regulate homeopathics. OTC homeopathic drugs containing labeling or advertising with unapproved health claims and labeled for indications requiring serious medical intervention require enforcement by the FDA. However, the vast majority of OTC homeopathic drugs are appropriately labeled and comply with FDA and HPUS requirements, and therefore NPA does not see the utility of holding homeopathic drugs to a new pre-approval process. New alternatives from FDA could involve implementation of a new regulatory paradigm through public notice-and-comment of final rulemaking to require a pre-approval gate for homeopathic drugs. While this has occurred in other countries, it has led to significant backlogs in the premarket authorization process. This would negatively impact consumer access to a wide range of homeopathic products on the market today. A better strategy for FDA is to remove harmful products from the marketplace using signals in case reports from FDA CDER AERS. NPA is also willing to work with FDA on developing guidelines for claims used to market OTC homeopathic products.

In terms of the agency's charge regarding public safety, GMPs and post-market surveillance provide the greatest ability to ensure the safety of the consumer. While FDA lists post-market surveillance of adverse events in its homeopathic enforcement guidance, it has always had the enforcement tools to remove unsafe products from the marketplace and protect public health. A new draft guidance on enforcement priorities is unnecessary and fails to convey critical information to industry. For example, the draft guidance fails to address how AERs will be used or how they have been used in the past to protect public health. Noticeably absent are the factors FDA will consider in determining whether a product labeled with a statement of identity as a "Homeopathic" will be viewed as an unapproved drug. The guidance contains few details to inform industry as to the criteria FDA plans to use in adjudicating whether a homeopathic product would be deemed to be an unapproved drug.

With regards to the appropriateness of this discussion through draft guidance (a document designed to convey the Agency's "thinking" on a subject), it would seem a more open and responsive format other than a draft guidance with defined comment period is necessary. This would be beneficial to the agency especially in light of current initiatives like the transparency task force. If the agency is making a policy shift in enforcement strategy away from sec. 400.400 of the FDA's CPG, more clarity on that shift will be needed for rational business and regulatory decisions to be made. FDA engaging the rulemaking process would keep FDA accountable to transparency to provide why it is they included certain comments into their new enforcement strategy and discarded other comments.

Should the guidance be referenced in enforcement activities many products now sold as homeopathic drugs may be considered illegal by the Agency, and any such changes to existing federal regulations cannot be made through the guidance process. These changes would have to be made through formal notice and comment rulemaking and be made in compliance with the APA. Going forward, the Natural Products Association reiterates its interest in partnering with FDA, to improve the way it applies enforcement discretion. NPA works closely with the Natural Product Foundation to bring enforcement cases to the attention of FDA CDER, FDA CFSAN, FDA's Health Fraud Coordinator, and FTC. NPF would be willing to work with FDA to bring better enforcement of low hanging fruit in the setting of limited resources of the Agency. Thank you for this opportunity to comment. We appreciate the opportunity for industry stakeholders to participate in this important comment period.

Respectfully submitted,

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