Natural Products ASSOCIATION™
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

RE: Docket No. FDA–2015–N–0540; Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century; Public Hearing; Extension of Comment Period

Dear Sir or Madam:

The Natural Products Association (NPA) is submitting this letter as general comment to docket FDA–2015–N–0540 (Docket Name: Homeopathic Product Regulation: Evaluating the Food and Drug Administration's Regulatory Framework After a Quarter-Century**)**. 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 of Mar. 30, 2015 (80 FR 16327), the Food and Drug Administration (FDA) published a 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 Federal Register announcement indicated that FDA would hold a public meeting on Apr. 20 and 21, 2015. FDA seeks 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.

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

[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).

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 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

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[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.

[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.

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 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 dilutions. The key element in the CPG was

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[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.

[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.

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.

[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).

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 enforcement policies set forth in the Agency's CPG entitled "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.

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]

[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

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.

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.

Homeopathics are Adequately Labeled for Consumers

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

18 http://www.accessdata.fda.gov/scripts/warningletters/wlSearchResult.cfm?qryStr=homeopathic+hcg&sortColumn=&Go=Go&webSearch=true

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

[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.

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 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]

[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.

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 toxicity,[30,31,32] allergies,[33,34,35,36,37,38,39] pediatric diarrhea,[40,41,42,43] psoriasis,[44] infection,

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[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.

[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.

inflammation[45,46,47,48,49,50,51,52,53] and pain.[54] This is an abbreviated list of the various conditions and symptoms for which homeopathic drugs have demonstrated some effect over placebo in RCTs.

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 seeks 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.

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

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[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.

[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.

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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 has a track record of success in the number of warning letters and enforcement actions taken over the past several years. 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 would implement 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 a 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.

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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