# COMMENTS

## OVER THE COUNTER, UNDER THE RADAR: HOW THE ZICAM INCIDENT CAME ABOUT UNDER FDA'S HISTORIC HOMEOPATHIC EXCEPTION

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TABLE OF CONTENTS



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## INTRODUCTION

On June 16, 2009, Matrixx Initiatives, Inc., maker of Zicam Cold Remedy products, received a devastating piece of correspondence. Arguably even more than the 300 lawsuits waged against Zicam products since 1999,[1] this letter had the potential to impact Matrixx's business like nothing else, short of a complete cure for the common cold. It was a warning letter from the Food and Drug Administration (FDA), alerting the manufacturer that due to over 130 reports of anosmia—loss of sense of smell, which in some cases can be long lasting or permanent—FDA concluded that Zicam intranasal products posed a serious risk to consumers.[2] The agency thus intended to regulate the intranasal products as "new drugs" under the applicable provision of the Federal Food, Drug, and Cosmetic Act (FDCA).[3] Marketed as homeopathic drugs, the products were never subject to FDA premarket approval, which requires prescription and over-the-counter (OTC) drugs not generally recognized as safe and effective to be thoroughly tested before entering the market.[4] Unlike Zicam

1. *See* Jennifer Corbett Dooren, *FDA Warns Against Use of Zicam*, WALL ST. J., June 17, 2009, at B1 (highlighting the safety issues that have plagued the company's intranasal products—Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Gel Swabs, and Zicam Cold Remedy Swabs Kids' Size—since their inception, and describing Matrixx's settlement of its numerous lawsuits in 2006); Valerie Jablow, *Lawsuits Sniff Out Zinc Hazard in Nasal Cold Remedy*, TRIAL, Feb. 2005, at 78 (listing some of the suits' claims which included fraud, negligence, strict products liability, breach of warranty, and breach of state consumer protection statutes).

2. *See* Letter from Deborah M. Autor, Dir., Office of Compliance, Ctr. for Drug Evaluation & Research, FDA, to William J. Hemelt, Acting President, CFO, and COO, Matrixx Initiatives, Inc. (Jun. 16, 2009), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm166909.htm [hereinafter Warning Letter] (noting that loss of sense of smell can have serious consequences, such as inability to detect the smell of a gas leak, smoke, or spoiled food; the letter also stated that some Zicam users also lost their sense of taste).

3. *Id.*; *see* Federal Food, Drug, and Cosmetic Act (FDCA) § 201(p), 21 U.S.C. § 321(p)(1) (2006) (defining *new drug* as any drug not generally recognized among qualified experts as safe and effective for its intended use).

4. *See* Warning Letter, *supra* note 2 (asserting that "[n]othing in the [FDCA] or the regulations issued under it exempts homeopathic drugs from new drug approval requirements," but recognizing that FDA has traditionally made the discretionary choice not to enforce the requirements with regard to homeopathic drugs); FDCA § 505(a), 21 U.S.C. § 355(a) (2006) (banning new drugs from introduction into interstate commerce without an

intranasal products, Zicam oral products have posed no safety threat, and thus remain on the market under FDA's historic homeopathic exception.[5] The warning letter prompted a voluntary recall projected to cost nearly $10 million, effectively eradicating the targeted products from the market unless and until Matrixx can prove them to be safe and effective for their intended uses under FDA's new drug application regime.[6] Not only did the market negatively respond to the warning letter—Matrixx stock plummeted 70% the day of the letter's release—but the media took issue with the situation as well, questioning the ability of a product to exist on drug store shelves with seemingly no FDA oversight.[7]

Consumers may be similarly troubled by the questions raised in the Zicam incident. Many consumer advocate websites attempt to warn the public that if an OTC product states "homeopathic" on the label, buyers may not be getting what they expect—a drug approved by FDA to be safe and effective for use as directed.[8] What may increase the severity of the Zicam situation is FDA's discovery of over 800 similar adverse event reports in Matrixx's possession that were never turned over to FDA.[9] For

approved new drug application); FDCA § 505(b)(1)(A), 21 U.S.C. § 355(b)(1)(A) (2006) (requiring all new drug applications to contain—and thereby conditioning their approval on—reports of investigations showing that the drug is safe and effective for its intended use).

5. *See generally* FDA, COMPLIANCE POLICY GUIDES § 400.400, CONDITIONS UNDER WHICH HOMEOPATHIC DRUGS MAY BE MARKETED (1988, revised 1995), *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074360.htm [hereinafter COMPLIANCE POLICY GUIDE] (setting forth the only comprehensive set of regulatory guidelines for the marketing of homeopathic drugs, including conditions under which FDA will discretionarily allow marketing of homeopathic drugs without approved new drug applications).

6. *See* Jonathan D. Rockoff, *Matrixx Receives SEC Inquiry Following Warning About Zicam*, WALL ST. J., June 24, 2009, at B3 (detailing the reactive measures Zicam was forced to take in the wake of the warning letter's publication, which included a pledge to reimburse consumers for prior purchases of Zicam intranasal products).

7. *See id.* (correlating the stock price drop with the large percentage of Matrixx's business that was represented by its Zicam intranasal products); Transcript for FDA Media Briefing on FDA's Advice to Consumers Not to Use Certain Zicam Cold Remedies, June 16, 2009, http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM168484.pdf (featuring questions from reporters of major news outlets to FDA representatives, some questions particularly focusing on the confusing regulatory posture of homeopathic drugs like the Zicam products).

8. *See, e.g.*, ConsumerReportsHealth.org, Homeopathic Drugs: Look-Alike Medicines, http://consumerreports.org/health/natural-health/homeopathic-drugs/overview/homeopathic-drugs-ov.htm (last visited Apr. 11, 2010) (citing the experience of eleven "mystery shoppers" who visited fifty-two drug stores across the United States and found homeopathic and approved OTC products directly next to each other on store shelves, purportedly demonstrating that it was conceivable for consumers to unwittingly buy a homeopathic product without understanding the significant differences between it and the neighboring approved product).

9. *See* Warning Letter, *supra* note 2 (acknowledging the existence of the 800 reports

the average consumer, a heightened concern regarding FDA's methods is understandable; yet the Zicam incident appears to be the first of its kind. The warning letters issued to homeopathic marketers in the past involved regulatory infractions, not serious adverse events.[10] In fact, this is precisely the reason cited by FDA for its discretionary lack of oversight—with a view to the agency's limited resources, homeopathic products have simply never aroused significant cause for concern—that is, until now.[11]

This Comment will examine the foundations of the current homeopathic drug regulatory framework, evaluate the strengths and weaknesses of FDA's seemingly hands-off approach, and provide an analysis of how FDA can preserve the system's strengths while incorporating more oversight into its homeopathic product regime. Although this Comment provides background on both prescription and OTC homeopathic drugs, the regulatory analysis and recommendations pertain strictly to the OTC class. Part I provides a background of homeopathy and its historic treatment by both Congress and FDA. Part II examines FDA's current system of homeopathic product regulation and its application to the Zicam incident in order to extrapolate the powers invoked by FDA and the implications of those powers on the homeopathic drug industry. Finally, Part III provides recommendations for a future approach to homeopathic drug regulation with a focus on how FDA can incorporate aspects of analogous regimes into its current system to better effectuate its purpose of protecting the public health. The goal of these recommendations is to find a balance between two somewhat competing goals: judicious allocation of limited FDA resources and protection of public consumers in their reasonable expectations of product safety.

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related to anosmia and requiring Matrixx to promptly submit the reports to FDA); *see also* Dooren, *supra* note 1 (explaining that although OTC product manufacturers were not required to report adverse events to FDA until recently, the legislation that implemented the requirement has been in effect since 2007). The FDA is still investigating these reports.

10. *See* Isadora Stehlin, *Homeopathy: Real Medicine or Empty Promises?*, FDA CONSUMER, Dec. 1996, at 15, 18 (finding that the most common infraction was the sale of prescription homeopathic drugs over the counter). Other warning letters cited products being "promoted as homeopathic that contain nonhomeopathic active ingredients"; "lack of tamper-resistant packaging"; "lack of proper labeling"; and "vague indications for use that could encompass serious disease conditions," which would require prescription dispensing and labeling. *Id.* For a more detailed discussion of the Compliance Policy Guide from which these violations stem, see *infra* Part II.

11. *See* Suzanne White Junod, *An Alternative Perspective: Homeopathic Drugs, Royal Copeland, and Federal Drug Regulation*, 55 FOOD & DRUG L.J. 161, 178–79 (2000) (recounting the reasoning behind the exclusion of homeopathic treatments from the OTC Drug Review, which included perceptions that such treatments were harmless and that homeopathy was a dying specialty).

## I. BACKGROUND

The cloud of ambiguity surrounding homeopathic drugs is best explained through the FDA regulatory framework, whose treatment of homeopathic products stems from a controversial history dating back to the enactment of the FDCA in 1938. Concomitantly, the best approach for FDA to address situations like the Zicam incident in the future must be charted within this framework in consideration of the policy issues that have shaped the current state of homeopathic drug regulation. This section provides a brief history of homeopathy and the historic development of homeopathic drug regulation in the United States.

### *A. What Is Homeopathy?*

The National Center for Complementary and Alternative Medicine (NCCAM) within the National Institutes of Health (NIH) designates homeopathy as a "whole medical system," or a complete system of theory and practice that evolved separately from "conventional medicine."[12] Homeopathy was developed by Samuel Hahnemann, a German physician practicing in the late 1700s, a time when bloodletting was the most common medical practice in Europe and the United States.[13] Hahnemann's aversion to the harsh and ineffective treatments of his day led him to seek out new forms of therapy, through which he developed the first, and main, tenet of homeopathy: like cures like, or the law of similars.[14] This premise holds that if a substance causes certain symptoms in a healthy person, the substance can treat those symptoms when exhibited by a person

12. NAT'L CTR. FOR COMPLEMENTARY & ALTERNATIVE MED., U.S. DEP'T OF HEALTH AND HUMAN SERVS., CAM BASICS 2 (2007), http://nccam.nih.gov/health/whatiscam/D347.pdf.

13. LYN W. FREEMAN & G. FRANK LAWLIS, MOSBY'S COMPLEMENTARY & ALTERNATIVE MEDICINE 347 (John Schrefer ed., 2001); Stehlin, *supra* note 10, at 16. Other popular treatments included blistering, which involved placing scalding substances on the skin to "draw out" infection, and administration of large doses of toxic substances, such as opiates, chloroform, and calomel (mercury chloride) to relieve pain and induce purging. *Id.*; NATALIE ROBINS, COPELAND'S CURE 6 (2005).

14. ROBINS, *supra* note 13, at 6. This founding homeopathic theory shaped the practice's name: "homeopathy" was derived from the Greek terms *homoios* (like) and *pathos* (suffering). Stehlin, *supra* note 10, at 16. Fittingly, Hahnemann referred to conventional medicine as "allopathy," from the Greek term *allos* (other). ROBINS, *supra* note 13, at 6. The term has stuck, and many sources still refer to conventional medicine as allopathy. The National Council Against Health Fraud insists that this term has been misapplied since the time of Hahnemann and asserts that modern medical writers who refer to conventional doctors as "allopaths" do so with an intended alternate meaning, one that refers to a practice utilizing only those remedies "proved of value." NAT'L COUNCIL AGAINST HEALTH FRAUD, NCAHF POSITION PAPER ON HOMEOPATHY (1994), http://ncahf.org/pp/homeop.html.

who is ill.[15] Hahnemann developed the theory when he experimentally administered himself a strong dose of quinine and found that it caused him to develop symptoms similar to those caused by malaria.[16] He tested his theory on himself and others in a practice he called "provings"—if a substance brought about certain symptoms, it would be used by homeopaths to treat those symptoms.[17] Hahnemann began to decrease the dosage of his test substances (which were debilitating in high quantities) and thereby developed the second main tenet of homeopathy: the minimum dose, or the law of infinitesimals.[18] This premise called for diluting homeopathic preparations to an extreme degree and subjecting them to forceful shakings between successive dilutions.[19] This practice has been unsparingly criticized. First, if any active ingredient remains in a preparation, it is, as the homeopathic principal describes, infinitesimal. For example, the amount of original substance in a 30X product has been diluted 1,000,000,000,000,000,000,000,000,000,000 times, which is roughly equivalent to one drop in a container more than fifty times the size

15. Stehlin, *supra* note 10, at 16. Some sources suggest that the idea of like cures like goes back to the writings of Hippocrates. *E.g.*, FREEMAN & LAWLIS, *supra* note 13, at 347; *see also* PHILLIP A. NICHOLLS, HOMEOPATHY AND THE MEDICAL PROFESSION 16–17 (1988) (placing the writings between 430 and 330 B.C.). However, Phillip A. Nicholls asserts that those writings were likely not authored entirely by Hippocrates, resulting in the use of both similars *and* opposites in the Hippocratic texts—use of medicines that were thought to bring about and medicines that were thought to suppress the symptoms expressed by the patient. *Id.*

16. Stehlin, *supra* note 10, at 16. Quinine had been used for centuries to treat malaria and fever but why it helped was not known. ROBINS, *supra* note 13, at 7. This invited Hahnemann to apply his theory to the substance's curative value, which he did for the smallpox vaccine as well. As an injection of cowpox, a form of the same illness the vaccine inoculated against, Hahnemann praised the vaccine as a prime example of the law of similars at work. ROBINS, *supra* note 13, at 6–7.

17. ROBINS, *supra* note 13, at 6. Homeopathy purported to treat symptoms, whereas allopathy purported to alleviate symptoms by treating the disease. *See* NICHOLLS, *supra* note 15, at 33 (analyzing the dual therapeutic methods from a socioeconomic standpoint, revealing that the orthodox approach stems from, among other things, an effort at streamlined disease-based diagnosing to treat more patients). Hahnemann believed that most recurring symptoms stemmed from a common disease, referred to as the "itch" or "psora." ROBINS, *supra* note 13, at 10.

18. Stehlin, *supra* note 10, at 16.

19. ROBINS, *supra* note 13, at 8–9. In this process, which Hahnemann called "potentization," one drop of substance is placed into a 1:10, 1:100, or 1:1000 ratio of water or alcohol, designated with Roman numerals as 1X, 1C, and 1M respectively. After the shaking or forceful hitting of the substance's container, called "succussion," one drop of the first dilution is then placed into a new 1:10, 1:100, or 1:1000 water or alcohol ratio, followed again by succussion. The process can be done once or repeated many times; the number of a substance's successive dilutions is indicated by the number in front of the Roman numeral X, C, or M. *See generally* FREEMAN & LAWLIS, *supra* note 13, at 350 (detailing the homeopathic dilution process).

of earth.[20] Second, at such high dilutions, there may not be any active ingredient in some preparations at all. Critics often cite Avogadro's number—which theorizes a point in the process of dilution where a molecule of any given substance can no longer exist—as evidence of the ineffectiveness of homeopathic products.[21]

Hahnemann developed the final tenet of homeopathy, the doctrine of individualized therapy, as a means of employing the first two: in practicing his new kind of medicine, he insisted that homeopaths conduct lengthy patient evaluations, often up to one or two hours, in order to ascertain all emotional and physical symptoms for precise treatment.[22] Through this practice and the absence of side effects resulting from diluted medications, homeopathy quickly gained publicity for employing a gentler approach than traditional medicine.[23] Conventional doctors continually outnumbered homeopathic practitioners; however, homeopathy remained popular with the public, resulting in over one hundred homeopathic medical schools in major cities across the country by the 1880s.[24] Around this time, the homeopathic community experienced a general, though not complete, shift away from strict adherence to certain classical homeopathic

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20. *See* Dan McGraw, *Flu Symptoms? Try Duck*, U.S. NEWS & WORLD REP., Feb. 17, 1997, at 51 (examining the popular homeopathic product oscillococcinum 200C, which uses the heart and liver of a single duck to create enough product to generate sales of over $20 million).

21. ROBINS, *supra* note 13, at 10. Several other unorthodox medical systems began to emerge in the United States around this time which must be distinguished from homeopathy. These include osteopathy, which holds that illness results from the failure of the body to have proper bone and muscle alignment; Christian Science, which believes that God alone promotes healing; chiropractic, which bases its healing on manipulation of the spine; and naturopathy, which purports to treat disease with natural elements, such as hot and cold air baths, massage, and diet. *Id.* at 24, 50.

22. W. STEVEN PRAY, A HISTORY OF NONPRESCRIPTION PRODUCT REGULATION 191 (2003); *see also id.* at 192 (pointing out that OTC homeopathic products, which obviously do not require individualized evaluation before purchase, violate this doctrine and thus "should not be considered homeopathic at all").

23. *See* ROBINS, *supra* note 13, at 5–6 (recounting that homeopathy was rumored to have greatly aided in the cholera epidemics of 1832 and 1849, which it likely did by replacing the harmful conventional treatment options of bloodletting and purging).

24. *See* Martin Kaufman, *Homeopathy in America: The Rise and Fall and Persistence of a Medical Heresy*, *in* OTHER HEALERS: UNORTHODOX MEDICINE IN AMERICA 99, 105 (Norman Gevitz ed., 1988) (noting that homeopathic and allopathic medical educations were very similar and that for the most part homoeopathic principals were taught in addition to, not in the place of, traditional medical training). Homeopathy's popularity led the American Medical Association to believe that people were being duped by homeopathic practitioner "gimmickry." ROBINS, *supra* note 13, at 19. This sentiment continues among critics today. *See, e.g.*, Leon Jaroff, *The Man Who Loves to Bust Quacks*, TIME, Apr. 30, 2001, at 61 (profiling Stephen Barrett, a former psychiatrist and well-known health fraud monitor who has dedicated thirty years to educating consumers on how not to be duped by "quacks" and their sales tactics, mainly on his widely read website entitled "Quackwatch").

laws, such as the practice of prescribing a single preparation for all of a patient's symptoms and the oxymoronic principle of the greater the dilution the more potent the preparation.[25]

One of the early death knells of homeopathic prominence in the United States was the widely publicized Flexner Report which surveyed the quality of medical education in the United States.[26] Its depictions of most homeopathic medical schools as subpar training facilities that were unscientific, even unsanitary, resulted in the majority closing or converting to allopathic medicine by the 1920s.[27] Another blow to homeopathy was dealt by the scientific advancements that abounded during the early- to mid-1900s, including the development of antibiotics as well as clinical studies utilizing placebos as controls to prove the effectiveness of medicines.[28] This progress greatly enhanced public desire for scientific medicine, leading to a significant decline in the practice and teaching of homeopathy in the late 1930s and early 1940s.[29]

Yet homeopathy has not gone away. The paradigm-shattering consciousness of the 1960s and 1970s saw a large increase in demand for all things unconventional, including medicine.[30] Today, homeopathy and many other forms of treatment are grouped together in the general category of complementary and alternative medicine (CAM), use of which continues to expand.[31] A recent survey by NIH and the Centers for

25. *See* Kaufman, *supra* note 24, at 106–07 (noting that homeopathic practitioners who streamlined their practices to combine homeopathy and allopathy were able to see more patients and thus increase their income, something the remaining "pure" Hahnemannian homeopaths reviled).

26. *Id.* at 111.

27. *Id.* at 112; ROBINS, *supra* note 13, at 111, 117.

28. ROBINS, *supra* note 13, at 123, 225.

29. *Id.* at 226. Dr. Morris Fishbein, editor of the *Journal of the American Medical Association* who would later become the Association's president, proclaimed "The Death of Homeopathy" as early as 1932, faulting Hahnemann's "unprovable theory." MORRIS FISHBEIN, FADS AND QUACKERY IN HEALING 27–29 (1932). Surmising this triumph, he wrote, "Thus passed the homeopathic system. Thus, in fact, pass all systems in the practice of medicine. Scientific medicine absorbs from them that which is good, if there is any good, and then they die." *Id.* at 28–29.

30. *See generally* Anne Taylor Kirschmann, *Making Friends for "Pure" Homeopathy: Hahnemannians and the Twentieth-Century Preservation and Transformation of Homeopathy*, *in* THE POLITICS OF HEALING: HISTORIES OF ALTERNATIVE MEDICINE IN TWENTIETH-CENTURY NORTH AMERICA 29 (Robert D. Johnston ed., 2004) (elaborating on the philosophical underpinnings of homeopathy which spurred the practice's reemergence when the 1960s counterculture identified with "pure" homeopathy's focus on individualized care and rejection of the mainstream medical establishment). *But see* ROBINS, *supra* note 13, at 241 (describing the time as one that brought homeopathy back into relevance, yet acknowledging that continual scientific advances would never allow homeopathy to escape the shadow of dominant conventional medicine).

31. *See* NAT'L CTR. FOR COMPLEMENTARY & ALTERNATIVE MED., *supra* note 12, at 1

Disease Control and Prevention found that Americans spend $34 billion a year on alternative therapies, a growth of more than 25% in the past decade.[32] The survey shows that $2.9 billion alone goes toward homeopathic products,[33] a number that gives new significance to the FDA warning letter to Matrixx by highlighting the obvious implications such enforcement actions pose to the homeopathic drug market.

### *B. Historic Congressional Treatment of Homeopathy*

The Federal Food, Drug, and Cosmetic Act of 1938 was the landmark legislation that established FDA's power of premarket review for all new drugs. It also represents the point at which homeopathy first made an appearance in the *United States Code*. One provision of the FDCA definition of the term *drug* includes "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."[34] FDA has generally not been able to regulate products as drugs based solely on their inclusion in one of the listed compendia, as the text appears to allow.[35]

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(defining *complementary medicine* as medicine used together with conventional medicine, and *alternative medicine* as medicine used in place of conventional medicine). NCCAM lists the following examples as falling under the CAM umbrella: acupuncture, aromatherapy, ayurveda, chiropractic, dietary supplements, electromagnetic fields, homeopathic medicine, massage, naturopathic medicine, osteopathic medicine, qi gong, reiki, therapeutic touch, and traditional Chinese medicine. *Id.* at 3–4.

32. Liz Szabo, *More Trying Alternative Therapies*, USA TODAY, July 31, 2009, at 3A. A 1998 study from the Stanford Center for Research in Disease Prevention found that "the majority of alternative medicine users appear to be doing so not so much as a result of being dissatisfied with conventional medicine but largely because they find these health care alternatives to be more congruent with their own values, beliefs, and philosophical orientations toward health and life." John A. Astin, *Why Patients Use Alternative Medicine: Results of a National Study*, 279 JAMA 1548, 1548 (1998); *see also Alternative Medicines: Hearing Before the Subcomm. on Labor, Health and Human Servs., and Educ., and Related Agencies of the S. Comm. on Appropriations*, 106th Cong. 1, 2 (2000) (opening statement of Sen. Arlen Specter, Chairman, Subcomm. on Labor, Health and Human Servs., and Educ., and Related Agencies of the S. Comm. on Appropriations) (citing statistics that showed 42% of United States health care consumers utilized CAM treatments and discussing the founding of NCCAM within NIH to promote studies on CAM treatments).

33. Szabo, *supra* note 32.

34. FDCA § 201(g)(1)(A), 21 U.S.C. § 321(g)(1)(A) (2006).

35. *See* Nat'l Nutritional Foods Ass'n v. FDA, 504 F.2d 761, 788–89 (2d Cir. 1974) (dismissing the argument that recognition in an official compendia is sufficient to establish that a product as falls under the "drug" definition because such a premise would lead to the conclusion that all vitamins and minerals are drugs because they are listed in the official compendia, which runs counter to FDA's own regulations); *see also* Nat'l Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 337–38 (2d Cir. 1977) (rejecting a similar FDA argument as arbitrary, finding that FDA's position would result in conflicting treatment of only certain vitamins as drugs despite other vitamin listings in the official compendia).

However, this provision has been the source of much confusion as to why the 1938 Act bothered to recognize the Homeopathic Pharmacopeia of the United States (HPUS) in the first place.[36] The common answer is that the senator who sponsored the FDCA, Royal Copeland, was a homeopathic physician, and it is undeniable that Copeland favored inclusion of the HPUS in the FDCA because of his affiliation with the practice.[37] However, FDA historian Susan White Junod asserts that food and drug officials likely welcomed this proposal, not as a concession to Copeland but as part of a strategy to utilize the FDCA to prosecute fraudulent drug salesmen that peddled bogus homeopathic products.[38]

Another provision of the *United States Code* that references the HPUS is the FDCA section that defines *official compendium*.[39] The import of this provision lays in those sections of the FDCA that state the conditions under which a drug is rendered adulterated or misbranded—the FDCA utilizes the official compendia for public standards of strength, quality, and

36. *See* Junod, *supra* note 11, at 161 (pointing out the incongruity of the FDCA representing the modernization of drug regulation yet simultaneously recognizing the seemingly unscientific and waning practice of homeopathy). According to the Homeopathic Pharmacopeia Convention of the United States (HPCUS), the entity now responsible for publication of the HPUS, the HPUS was first published in 1897 and continues to be a source of homeopathic drug information, including drug monographs, general labeling, and manufacturing information. HPCUS, What is the HPUS?, http://www.hpus.com/whatishpus.php (last visited Apr. 11, 2010); HPCUS, Overview, http://www.hpus.com/overview.php (follow "The HPUS Revision Service Contents" hyperlink) (last visited Apr. 11, 2010). The official version of the HPUS is now referred to as the HPUS Revision Service, which is available only in web format through an online subscription via www.hpus.com.

37. *See* ROBINS, *supra* note 13, at 207 (describing the inclusion of the HPUS in the FDCA as a part of Copeland's lifelong effort to enhance homeopathy's legitimacy in society). Senator Copeland, who had served as dean of the New York Homeopathic Medical College and as the New York Health Commissioner, rejected much of the mysticism that accompanied early homeopathic doctrine and was at the fore of the homeopathic modernization movement. *See id.* at 100, 148–50, 166–67 (detailing the influential positions held by Copeland including his fortuitous election as New York State Senator in 1922, which was largely a product of his prominence in the health field); Junod, *supra* note 11, at 167 (describing Copeland's explanation of homeopathy as a "complementary medical discipline" to be used in conjunction with advancing science, and his downplaying of the law of infinitesimals).

38. *See* Junod, *supra* note 11, at 173–74 (contending that this strategy is one the legislators would have purposely withheld from the legislative record, and pointing out that, indeed, the record gives no reasoning behind inclusion of the HPUS in the 1938 Act where the 1906 Pure Food and Drugs Act already recognized the United States Pharmacopoeia and the National Formulary as official compendia).

39. FDCA § 201(j), 21 U.S.C. § 321(j) (2006). The other official compendia, the United States Pharmacopeia (USP) and the National Formulary (NF), are now published together in a single volume referred to as the USP–NF.

purity.[40] The HPUS was likely included in the "official compendium" definition as a result of its inclusion in the "drug" definition; however, the HPUS has historically been relied on to a very limited extent in the context of both FDCA provisions: FDA officials have always had many other tools under the Act by which to halt sales of bogus products claiming to be based on homeopathic theory, and legitimate homeopathic drugs historically have not posed safety threats, obviating use of the HPUS language in the Act.[41] The *United States Code*'s formal recognition of homeopathy has therefore had little impact—likely the reason the HPUS remains in the text today.[42]

### *C. Historic FDA Treatment of Homeopathic Drugs*

FDA's interpretation and application of legislative amendments to the FDCA—as opposed to the statutory language itself—has been the main source of regulation historically governing homoeopathic products. The first wave of regulation that significantly affected the homeopathic community was the 1951 Durham–Humphrey Amendment to the FDCA.[43] The amendment states that if use of a drug is unsafe unless

40. *See* PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, FOOD AND DRUG LAW 534 (3d ed. 2007) (explaining that if a drug fails to comply with the official compendium standard, the manufacturer may still use the common drug name listed in the compendium and state how the drug differs from the standard in strength, quality, or purity). If a drug is included in both the USP–NF and the HPUS, the USP–NF standards apply unless the product is clearly labeled and sold as a homeopathic product. FDCA §§ 501(b), 502(e), 502(g), 21 U.S.C. §§ 351(b), 352(e), 352(g). Although still an official compendium whose standards homeopathic drugs must generally conform to, the HPUS has played a more limited role in FDA adulteration and misbranding regulation than the USP–NF because of the limited nature of homeopathic drug regulation generally. *Cf.* Edward M. Cohen, *The Influence of the USP on the Drug Approval Process*, *in* THE PHARMACEUTICAL REGULATORY PROCESS 335, 335–39 (Ira R. Berry & Robert P. Martin eds., 2d ed. 2008) (detailing the development of the USP and its extensive historical involvement in FDA statutory enforcement schemes, which expanded with its acquisition of the NF in 1974).

41. *See* Junod, *supra* note 11, at 175–76 (citing the FDA's new authority under the 1938 Act to conduct factory inspections as a more straightforward approach to apprehending fraudulent product manufacturers); ROBINS, *supra* note 13, at 7–8 (revealing that many substances used in homeopathic products were used by ancient civilizations, and, in any event, homeopathy advocates believed that even potentially toxic substances were seldom dangerous at such high dilutions).

42. *See* Junod, *supra* note 11, at 179 (recounting that the proposed 1979 Drug Reform Act would have eliminated the HPUS provisions; however because the bill was defeated and no House hearings were held, the reasoning behind the proposal remains unclear and the HPUS remains in the statute).

43. *Id.* at 176; *see also* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 488–90 (discussing the text of the amendment that codified FDA regulations distinguishing between prescription and nonprescription drugs). FDA's prescription requirement was based on the premise that adequate directions for use could not be formulated for certain drugs, which

supervised by a licensed practitioner because of its toxicity, other potentiality for harm, its method of use, or the collateral measures necessary to its use, the drug must be dispensed by prescription only.[44] After the law's passage, the leading homeopathic medical association, the American Institute for Homeopathy (AIH), advocated for most homeopathic drugs to be dispensed by prescription to keep in line with the traditional homeopathic practice of individualized treatment.[45] FDA approved, reservedly, stating that although the amendment did not appear to bring homeopathic drugs under its regime, FDA had no objection to their distribution with the prescription legend.[46] FDA was careful to note, however, that it would not bring enforcement actions against homeopathic

thus required dispensing and supervision by a medical practitioner. *See* Peter Temin, *The Origin of Compulsory Drug Prescriptions*, 22 J.L. & ECON. 91, 99 (1979) (noting that FDA never stated its reasoning behind this presumption, which inevitably had a great impact on the drug market).

44. FDCA § 503(b)(1), 21 U.S.C. § 353(b)(1) (2006). The original 1951 provision included "habit-forming" in the definition, which was deleted in 1997. HUTT, MERRILL & GROSSMAN, *supra* note 40, at 489. What constitutes a "licensed practitioner" is determined by each state as an inherent police power. MICHAEL H. COHEN, COMPLEMENTARY & ALTERNATIVE MEDICINE: LEGAL BOUNDARIES AND REGULATORY PERSPECTIVES 24 (1998). This policy was determined by the Supreme Court in *Dent v. West Virginia*, 129 U.S. 114 (1889), which held that the power of the states to provide for the general welfare authorizes state regulation of the medical profession to protect citizens from "ignorance and incapacity . . . deception and fraud." *Id.* at 122. *See generally* Michael H. Cohen, *A Fixed Star in Health Care Reform: The Emerging Paradigm of Holistic Healing*, 27 ARIZ. ST. L.J. 79 (1995) [hereinafter Cohen, *A Fixed Star*] (discussing the advent of medical licensing statutes in the United States and their function in entrenching traditional medical practices while excluding complementary and alternative medicine). Three states—Connecticut, Arizona, and Nevada—have established licensing boards for homeopathic practitioners; some states that do not have separate licensing boards nevertheless include homeopathy within the definition of complementary and alternative medicine (CAM) providers, who are subject to a licensing process, and other states limit the practice of homeopathy to licensed chiropractors only. *See* Patrick L. Sheldon, *The Truth About Homeopathy: A Discussion of the Practice and the Dangers That Inhere*, 8 QUINNIPIAC HEALTH L.J. 289, 295–97 (2005) (describing the range of restrictiveness in regulatory licensing regimes employed by the states, into which the professional practice of homeopathy falls differently from state to state).

45. *See* Junod, *supra* note 11, at 176–77 (describing the American Institute for Homeopathy (AIH) lobbying of FDA officials that resulted in most homeopathic drugs becoming prescription drugs in the 1950s). This was perhaps an effort on the part of AIH to establish integrity and legitimacy for a practice that, at the time, was a faint voice in the medical community.

46. *See id.* (asserting that FDA accepted the AIH's argument that adequate directions for use of homeopathic drugs could not be devised, in accordance with the theory behind the FDCA's prescription drug provision and the concomitant FDCA requirement that all OTC products contain adequate directions for use); *cf. id.* at 168 (recalling that prior to passage of the FDCA and its "adequate directions for use" provisions, a distinct benefit of homeopathic physicians was that they usually dispensed their own medicines, a practice that appealed to consumers who claimed pharmacists failed to provide satisfactory label directions).

products that were sold for minor conditions without a prescription, i.e., OTC homeopathic products, and it appears the homeopathic drug prescription labeling requirement was historically not strictly enforced.[47]

A far more serious alteration of the FDCA occurred with the Kefauver–Harris Amendments of 1962, which threatened to wipe homeopathic drugs from the market with a new requirement for proof of drug efficacy for intended uses.[48] Under the 1938 Act, drug makers were required to submit new drug applications (NDAs) to FDA demonstrating a drug's safety.[49] An NDA went into effect within approximately two weeks unless FDA took affirmative action against it, allowing the NDA drug as well as subsequent chemically similar products—or "me-too" drugs—to be marketed.[50] Under the 1962 Amendments, however, not only was affirmative approval required before a new drug could be marketed, but the Secretary was also required to reject an NDA or rescind a previously approved NDA if there was lack of substantial evidence of the drug's effectiveness.[51] Under these Amendments, FDA commenced the Drug Efficacy Study Implementation (DESI) by which it undertook to ascertain the efficacy of all drugs that were covered by former safety NDAs.[52] More importantly for the homeopathic community, FDA also undertook the large task of the Over-the-Counter Drug Review. Unlike the DESI Review that examined each individual 1938–1962 NDA-covered drug, and did so solely to determine efficacy for intended uses, the OTC Drug Review was conducted on a therapeutic category basis by which FDA advisory panels examined information on active ingredients, not individual OTC products, and did so to determine

47. *See id.* at 177 (revealing that this lack of enforcement was reportedly due to some FDA officials believing that the prescription legend lent "undeserved credibility" to homeopathic drugs).

48. *See generally* PRAY, *supra* note 22, at 147–70 (detailing the legislative history of the 1962 Act and how the thalidomide tragedy, where a sleeping pill approved in Europe caused birth defects in thousands of children, contributed to the passage of the premarket approval regime and its retroactive efficacy requirements).

49. 21 U.S.C. § 355(a)–(b) (1940).

50. *Id.* at § 355(c); *see also* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 579–80 (explaining that the original NDA drug was referred to as the "pioneer" and that all subsequent copy drugs had to correspond with an approved pioneer NDA, which was then said to "cover" all the "me-too" drugs as well).

51. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781 (1962) (inserting "and effectiveness" in various provisions within FDCA § 505 and setting forth the § 505(d) criteria by which an NDA is to be approved and the § 505(e) criteria by which an NDA is to be withdrawn—both provisions contain the language "lack of substantial evidence that the drug will have the effect it purports or is represented to have").

52. *See* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 580 (highlighting that industry members protested the idea of FDA examining 1938–1962 NDAs for efficacy and demanded an outside authority conduct examinations, resulting in FDA's contract with the National Academy of Sciences to conduct testing for the DESI Review).

both safety and efficacy for intended uses.[53] Drugs that did not meet FDA safety and efficacy standards were deemed "unapproved new drugs" and subjected to the NDA provisions of the FDCA; drugs that met the standard could remain on the market on the condition that they complied with published regulatory monographs specific to each active ingredient on issues such as dosing, labeling, warnings, and other important issues.[54]

By the time the OTC Drug Review commenced in 1972, approximately one-third of all homeopathic products sold were OTC.[55] However, with a view to limited FDA resources and the mounting work to be done on nonhomeopathic OTC products, FDA decided not to subject homeopathic drugs to review for safety and efficacy.[56] There appear to have been several unstated reasons for FDA's decision. First, homeopathic products generally did not pose serious safety threats.[57] Second, FDA was focusing its regulatory efforts elsewhere—not only on the OTC Drug Review, but on a large-scale attempt to regulate vitamins and minerals—and may have considered it impracticable to review homeopathic drugs at the time, or at least of little benefit in relation to the effort that would have been required.[58] And finally, FDA may have realized that homeopathic drug efficacy testing would be problematic from the outset. Commentators have

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53. *See generally* Over-the-Counter Drugs: Proposal Establishing Rule Making Procedures for Classification, 37 Fed. Reg. 85, 86–89 (Jan. 5, 1972) (describing FDA's reasoning for the OTC Drug Review); Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. 9464, 9464–73 (May 11, 1972) (the final rule, as amended, is now codified at 21 C.F.R. § 330.10) (addressing comments regarding the unique process by which OTC drugs would be reviewed).

54. *See* Over-the-Counter Drugs: Proposal Establishing Rule Making Procedures for Classification, 37 Fed. Reg. at 85 (introducing the monograph enforcement approach).

55. Junod *supra* note 11, at 178. AIH's attempt to relegate homeopathic drugs to the prescription domain had apparently failed.

56. *See* Over-the-Counter Drugs: Proposal Establishing Rule Making Procedures for Classification, 37 Fed. Reg. at 85–86 (noting the indomitable size of the OTC Drug Review, which encompassed between 100,000 and 500,000 OTC products containing an estimated 200 active ingredients). In the lengthy Procedures for Classification of Over-the-Counter Drugs, FDA dedicated a short and decisive paragraph to the issue:

> The American Institute of Homeopathy requested that homeopathic medicines be excluded from the OTC review. Because of the uniqueness of homeopathic medicine, the Commissioner has decided to exclude homeopathic drugs from this OTC drug review and to review them as a separate category at a later time after the present OTC drug review is complete.

37 Fed. Reg. at 9466. In the thirty-seven intervening years since this regulation, the plan to review homeopathic drugs has never materialized.

57. *See* Junod, *supra* note 11, at 177–79 (representing that FDA made a judgment call that, at the time, homeopathic products were not used nearly to the extent that other OTC products were used, and thus they were less of a concern for FDA in light of a history of relative safety).

58. *See id.* at 178–79 (asserting that FDA's preoccupation with the vitamin regulation, which eventually failed, made it easier for FDA to ignore homeopathic drugs).

suggested that due to the need to rely on the HPUS as an official compendium of homeopathic drug standards, any form of a homeopathic drug review may require drug testing by homeopathic experts using provings as efficacy tests.[59] FDA might have considered it imprudent to expend the resources necessary for another review that would have so vastly differed in approach from the scientific foundations of the OTC Drug Review.[60] In 1972, these very compelling reasons resulted in FDA leaving homeopathy well enough alone; that is, until 1988 when it issued the Compliance Policy Guide that governs sales of homeopathic drugs today.

## II. CURRENT HOMEOPATHIC DRUG REGULATION AND THE ZICAM INCIDENT

The driving force behind the warning letter to Matrixx is FDA's power under the FDCA to regulate a product as a drug if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or, for any product that is not food, if it is "intended to affect the structure or any function of the body."[61] The intended use of Zicam intranasal products, as

59. *See, e.g.*, *id.* at 177 (reasoning that scientific experts would apply standards incompatible with the official homeopathic compendium, the HPUS, which would be contrary to the language of the FDCA); Rebecca Gelfond, Regulating Homeopathic Drugs: Pragmatic Solutions for the Food and Drug Administration 44 (Feb. 8, 1999) (unpublished manuscript, on file with author), *cited in* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 619 (proposing that FDA require homeopathic drugs to be effective where effectiveness is viewed from the standpoint of homeopathy).

60. *See* 21 C.F.R. § 330.10(a)(4)(ii) (2009) (setting forth the Review's efficacy standard as a reasonable expectation that the pharmacological effect of the drug will provide clinically significant relief in a significant proportion of the target population). HPUS monographs were developed by homeopaths through traditional homeopathic provings, which themselves followed traditional homeopathic practices of dilution and succussion. These processes, and the homeopathic theories on which they rely, do not lend themselves to scientific evaluation, which is exactly what the AIH maintained in its discussions with FDA. *See* Kaufman, *supra* note 24, at 118 (depicting the homeopathic position as hostile to the OTC Drug Review process on the basis that homeopathic drugs could not be evaluated by "allopathic review"). Further, even in the unlikely event that FDA was comfortable relying on homeopathic provings as an acceptable form of efficacy testing, it is doubtful such tests would satisfy the Review's evidentiary requirement: the premise of like cures like may not scientifically comport with the intended meaning behind "clinically significant relief," 21 C.F.R. § 330.10(a)(4) (2006), and this ambiguous standard means it would be difficult for FDA to logically affirm that there was a "reasonable expectation" of achieving it. *Id.*

61. FDCA § 201(g)(1)(B)–(C), 21 U.S.C. § 321(g)(1)(B)–(C) (2006). The FDA has exercised this power to regulate products that were not generally considered drugs but that fell under the FDCA definition when manufacturers made drug-like claims demonstrating an intent that the products be used in the way the Act contemplates. *See, e.g.*, Letter from W. Charles Becoat, Dir., FDA Minneapolis District, to Ken Powell, Chairman and CEO, General Mills, Inc. (May 5, 2009), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm162943.htm (alerting the prominent food manufacturer that FDA would regulate Cheerios as a new drug

stated on the product labeling, was reduction of the duration of the common cold and the severity of cold symptoms, including sore throat, stuffy nose, sneezing, coughing, and congestion.[62] This means that the products were intended for use in the mitigation and treatment of disease, as well as intended to affect the function of the body, and thus were drugs under the FDCA.[63] Further, the warning letter asserts that the products are not generally recognized as safe and effective for their intended uses, which makes them not only drugs but also new drugs, for which approved NDAs are required.[64] Zicam intranasal products, like all homeopathic OTC products, always fell into this definition as a formal matter because they were never subjected to definitive safety and efficacy testing. Yet homeopathic products have been allowed to be marketed despite this fact due to, first, their exemption from the OTC Drug Review and, second, FDA's issuance in 1988 of a Compliance Policy Guide (CPG) that specifically allows such marketing. This CPG serves three main functions: (1) it establishes the conditions under which homeopathic drugs may be marketed, which do not include premarket NDA approval or compliance with an OTC drug monograph; (2) it warns the industry of how and when sale of a purportedly homeopathic drug will constitute health fraud; and (3) it sets forth specific regulations applicable to homeopathic products, including labeling requirements within the CPG as well as other requirements mandated by the FDCA and the *Code of Federal Regulations* (CFR).[65] This section will examine the CPG and analyze how these governing regulations applied to, and were invoked against, Zicam intranasal cold remedy products.

### *A. Conditions Under Which Homeopathic OTC Drugs May Be Marketed*

Under the CPG, to qualify as a homeopathic drug a product must (1) be labeled as homeopathic; (2) contain an active ingredient listed in the HPUS; (3) be in a potency specified in terms of dilution, e.g. 1X, 2C, etc.; (4) contain diluents commonly used in homeopathic pharmaceuticals; and

based on labeling on the box and website indicating an intended use for the prevention, mitigation, and treatment of hypercholesterolemia—excessive cholesterol—and the correlative coronary heart disease).

62. Warning Letter, *supra* note 2.

63. FDCA § 201(g)(1)(B)–(C), 21 U.S.C. § 321(g)(1)(B)–(C) (2006). Zicam intranasal products are not drugs based solely on their active ingredient's inclusion in the HPUS. *See supra* note 35 (describing why the official compendia provision of the drug definition cannot be taken literally).

64. Warning Letter, *supra* note 2; FDCA § 201(p)(1), 21 U.S.C. § 321(p)(1) (2006).

65. COMPLIANCE POLICY GUIDE, *supra* note 5, at 105–06.

(5) not be combined with any nonhomeopathic active ingredients.[66] Matrixx's Zicam intranasal products strictly complied with these CPG requirements: the packaging stated "Homeopathic";[67] the drug's only active ingredient, zinc gluconate, is included in the HPUS;[68] the ingredient was displayed on the labeling as "zincum gluconium 2X";[69] and the substance was diluted with water and other inactive ingredients providing the gel-like texture.[70] However, as the warning letter makes clear, compliance with the CPG does not preclude FDA action.

The CPG further mandates that products offered for the treatment of serious disease conditions be dispensed under the care of a licensed practitioner.[71] The key to the intended meaning of *serious disease condition* within the CPG is what the CPG allows to be sold *without* a prescription—products offered for use in "self-limiting conditions" that are recognizable by consumers and amendable to self-diagnosis.[72] Therefore, any drug that

66. *Id.* Diluents are generally water, alcohol, or both combined. HOMEOPATHIC PHARMACOPEIA CONVENTION OF THE U.S., THE HOMEOPATHIC PHARMACOPOEIA OF THE UNITED STATES REVISION SERVICE (online subscription, Dec. 2004), http://www.hpus.com [hereinafter HPUS REVISION SERVICE]. The HPUS lists several types of alcohols that may be used, including ethyl alcohol (found in alcoholic beverages), sucrose, lactose, and glycerin (which are all sugar alcohols). *Id.* Orally ingested homeopathic drugs are exempted from regulations mandating that OTC drugs intended for oral ingestion not contain alcohol as an inactive ingredient above certain prescribed concentrations. 21 C.F.R. § 328.10(a), (g)(3) (2009).

67. *See* MedShopExpress, Zicam No-Drip Liquid Nasal Gel, Cold Remedy Swabs, http://www.medshopexpress.com/602163.html (last visited Apr. 11, 2010) (providing a product description which includes detailed labeling text and a picture of the product packaging).

68. *Id.*; *see* HPUS REVISION SERVICE, *supra* note 66 (featuring the zinc gluconate monograph).

69. MedShopExpress, *supra* note 67. The designation 2X indicates that the product was diluted 1:10 twice, leaving 1 part per hundred (1:100 or 1 percent) of zinc gluconate in the final product. For an explanation of the homeopathic dilution process and the roman numeral designations, see *supra* note 19.

70. MedShopExpress, *supra* note 67.

71. COMPLIANCE POLICY GUIDE, *supra* note 5, at 105. For the meaning of *licensed practitioner*, see *supra* note 44.

72. COMPLIANCE POLICY GUIDE, *supra* note 5, at 105. The term *self-limited* is generally defined outside of the CPG as "limited by . . . its own nature" and "running a definite and limited course." WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 2060 (1986). This definition squarely applies to cold symptoms, minor aches and pains, sleeplessness, and other similar conditions for which OTC products are generally sold. Conversely, this definition would not apply to infectious diseases, such as strep throat or chlamydia, or life-threatening conditions such as cancer or AIDS. The CPG states that the prescription drug provision of FDCA is also applicable; therefore, any homeopathic drug that is unsafe if used without medical supervision due to its toxicity or other potential danger, including lack of adequate directions for use, is forbidden from OTC sale. Another provision of the CPG mandates that if the HPUS specifies certain distinctions between nonprescription and prescription status based on strength of the product, then the stricter criteria—either the prescription

is intended to treat a non-self-limiting condition must be dispensed by prescription. The Zicam products, again, strictly complied with these requirements, claiming only to reduce the duration and symptoms associated with the common cold—a classic example of a self-limiting condition.[73]

Notably, the CPG does not generally require NDA approval or compliance with an OTC drug monograph. The CPG is explicit in stating that all products falling within the drug definition are drugs under the FDCA regardless of whether they are homeopathic,[74] yet there is no mention of a homeopathic drug ever constituting a new drug under the FDCA, and there is no requirement for proof of safety or efficacy.[75] In the warning letter to Matrixx, however, FDA cites to a clause in the CPG that preserves its power of enforcement of the FDCA new drug provisions.[76] The clause asserts that the CPG delineates "those conditions under which homeopathic drugs may *ordinarily* be marketed in the [United States]."[77] Thus, as FDA interprets this clause in the warning letter, a homeopathic drug "is not subject to the enforcement discretion set forth in the CPG when there is evidence of a safety risk associated with the product."[78]

In order to effectively invoke the new drug provisions of the FDCA in the warning letter, FDA needed to show that the active ingredient in Zicam intranasal products was not generally recognized as safe and effective for its intended use.[79] The active ingredient in question—zinc gluconate—is a common ingredient in vitamins and dietary supplements.[80] To effectively

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drug provision of the FDCA or the listing in the HPUS—will apply to determine prescription status. COMPLIANCE POLICY GUIDE, *supra* note 5, at 108.

73. *Cf.* Anne Gadomski, *A Cure for the Common Cold?: Zinc Again*, 279 JAMA 1999, 2000 (1998) (advising medical practitioners to give patients balanced information on the effectiveness of zinc in treating the common cold because no alternative therapies have the weight of evidence behind them and the benign nature of the cold, which inevitably ceases on its own, does not necessitate drug treatment).

74. This position was confirmed in *United States v. Writers & Research, Inc.*, in which the court held that a product labeled as homeopathic that was being promoted as a treatment for cancer, AIDS, and other chronic and degenerative diseases was subject to the requirements of the FDCA regardless of its homeopathic status. 113 F.3d 8, 11 (2d Cir. 1997).

75. COMPLIANCE POLICY GUIDE, *supra* note 5, at 107.

76. Warning Letter, *supra* note 2.

77. COMPLIANCE POLICY GUIDE, *supra* note 5, at 106 (emphasis added).

78. Warning Letter, *supra* note 2. The warning letter also deemed Zicam misbranded because its labeling did not bear adequate warnings of the risk of anosmia. *Id.*

79. *See* FDCA § 201(p), 21 U.S.C. § 321(p) (2006) (defining *new drug* as a drug not generally recognized as safe and effective for its intended use); FDCA § 505(a), 21 U.S.C. § 355(a) (prohibiting the introduction of new drugs into interstate commerce without an approved NDA).

80. *See* Gadomski, *supra* note 73, at 1999 (comparing the use of zinc in attempts to

eliminate Matrixx's ability to claim that zinc gluconate is generally recognized as safe and effective based on such common oral ingestion, the warning letter points to the existence of published literature that salts of zinc can damage olfactory function.[81] Throughout the FDCA, the terms *safety* and *efficacy* are couched with the phrase *for intended use*—this makes safety for oral ingestion irrelevant if the same ingredient is unsafe for a different use, in this case intranasal application.[82]

### *B. When Sale of a Homeopathic Drug May Constitute Health Fraud*

The CPG only briefly mentions health fraud, yet it is an important inclusion in the face of the many complaints waged against the homeopathic regulatory regime.[83] The CPG defines *health fraud* as the "deceptive promotion, advertisement, distribution or sale" of drugs that are

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"cure the common cold" with vitamins C and A, noting that all have "immune-enhancing properties"). Pursuant to the Dietary Supplement Health and Education Act of 1994, dietary ingredients in dietary supplements are regulated as a special subset of foods under the FDCA which are not subject to premarket approval. *See* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 261–62 (describing the wide latitude dietary supplements achieved in the legislation that was enacted over FDA's strong objections); FDCA § 201(ff)(1)–(2), 21 U.S.C. § 321(ff)(1)–(2) (2006) (defining *dietary supplement* to include vitamins, minerals, herbs or other botanicals, amino acids, and any other dietary substance used to supplement the diet that is not represented as a conventional food). Zicam zinc-based products for oral ingestion have remained on the market as homeopathic products; however, their counterparts in the market—other orally ingested OTC cold drugs containing zinc—mostly fall under the dietary supplement regime. *See, e.g.*, Airborne, What's in Airborne, http://airbornehealth.com/about/whats-in-airborne (last visited Apr. 11, 2010) (listing the ingredients, including zinc, of the popular dietary supplement marketed to boost immunity to prevent or treat the common cold). The Zicam intranasal products could never qualify as dietary supplements due to the statutory definition of *dietary supplement* that specifies "ingestion" as the method of administration. FDCA § 201(ff)(2)(A)(i), 21 U.S.C. § 321(ff)(2)(A)(i) (2006); *see* United States v. Ten Cartons Ener-B Nasal Gel, 888 F. Supp. 381, 395 (E.D.N.Y. 1995) (holding that a Vitamin B-12 gel designed to be applied to the inside of the nose did not qualify for regulation as a dietary supplement because it was not "intended for ingestion," which implies administration through swallowing and entrance into the gastrointestinal tract).

81. Warning Letter, *supra* note 2.

82. The OTC monograph listing active ingredients found to be safe and effective for the uses indicated in Zicam product labeling—"Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use"—does not include zinc. 21 C.F.R. § 341 (2009).

83. *See, e.g.*, ConsumerReportsHealth.org, *supra* note 8 (suggesting that consumer confusion between homeopathic products and more stringently regulated OTC products is a result of misleading marketing that is characteristic of health fraud). The Federal Trade Commission, not FDA, is responsible for regulating false advertising of OTC products, as distinguished from the fraudulent products themselves. HUTT, MERRILL & GROSSMAN, *supra* note 40, at 809–10. But the agencies often work in concert on such issues and have memoranda of understanding promoting collaboration. *Id.* at 810.

"represented as being effective" but which have not been scientifically proven as such.[84] Critics would be quick to point out the irony of such a provision appearing in a homeopathic drug guidance when homeopathic products have never been, and may never be, proven effective by FDA standards.[85]

The health fraud provision explicitly deems products that follow the "customary practice of homeopathy" as not constituting health fraud.[86] This could mean one of two things. On one hand, FDA may be indicating a willingness to consider homeopathic provings to be scientific evidence of safety and efficacy. On the other hand, the provision may be a simple recognition of the cognitive dissonance FDA must employ to uphold the current state of its regulation, by which homeopathic drugs are freely sold without any form of review or approval. This latter interpretation is far more probable—the CPG's inclusion of the health fraud provision was most likely intended to reinforce the CPG's policy of voluntary discretion not to enforce the FDCA, which FDA is free to disregard in cases of patently fraudulent behavior by drug manufacturers.

### *C. Labeling Requirements and Other Regulations Applicable to Homeopathic OTC Drugs*

The CPG's general labeling requirements for homeopathic drugs reference provisions governing drugs in general in the FDCA and FDA-promulgated regulations. For example, the requirement for a "Name and Place of Business" on homeopathic product labeling must be carried out "in conformance with" the specific requirements for all other "name and place of business" drug labeling found in the FDCA and the CFR.[87] These provisions of the CPG are the reasons for the similarity between

84. COMPLIANCE POLICY GUIDE, *supra* note 5, at 106.

85. *See infra* part III.B (discussing the fact that homeopathic drugs would be eliminated from the market if a homeopathic drug efficacy review were instated). The CPG contains definitions of *homeopathy* and *homeopathic drugs*, and it cites two books that are offered as guides to the use of homeopathic drugs, including "potencies, dosing, and other parameters." COMPLIANCE POLICY GUIDE, *supra* note 5, at 106, 107. These resources are intended to give FDA officials a general understanding of how to differentiate between a genuine and a bogus homeopathic drug, though many would argue they are one and the same.

86. COMPLIANCE POLICY GUIDE, *supra* note 5, at 106.

87. *See id.* at 107 ("Each product must bear the name and place of business of the manufacturer, packer, or distributor in conformance with Section 502(b) of the [FDCA] and 21 CFR 201.1."). The CPG has similar labeling requirements for "Directions for Use," "Statement of Ingredients," "Established Name," and "Container Size" that apply to all homeopathic drugs, prescription and OTC. OTC homeopathic products in particular have other referential requirements for "Principal Display Panel," "Statement of Identity," "Indications for Use," and specific warning requirements for different indications that conform to OTC drug regulations. *Id.* at 107–08.

homeopathic and conventional OTC drug packaging; they are presumably a reflection of what FDA has determined to be necessary OTC labeling. The CPG also lists additional requirements specific to homeopathic products that are not found in the FDCA or the CFR: (1) the quantity and amount of ingredients in the product must be expressed in homeopathic terms, e.g., 1X, 2C, etc.; (2) if products or ingredients are not recognized by the HPUS, documentation must be provided to FDA to support that the products or ingredients are "generally recognized as homeopathic"; and (3) all labeling must be in English but may include the Latin name of the active ingredient in addition to the English name.[88]

These requirements have been the topic of much debate. The difference between conventional and homeopathic OTC drug labeling is essentially the word *homeopathic* and the listing of the active ingredient(s) in terms of dilution, as opposed to traditional units of measurement. On one hand, the CPG labeling requirements are beneficial in ensuring that the labels of homeopathic products include basic information that FDA considers necessary on all OTC drugs. On the other hand, such labeling may serve to confuse consumers as to what kind of product they are purchasing. If consumers do not notice the word *homeopathic* on the product label, or if they are unaware of what it means, they are likely to assume that the OTC drug has been tested for safety and efficacy by FDA (and that *efficacy* has its

88. *Id.* at 107. The requirement for supporting documentation for non-HPUS products presumably addresses the issue of manufacturers attempting to evade regulation by labeling a nonhomeopathic product as homeopathic. This has been the subject of warning letters to homeopathic drug manufacturers where FDA was quick to go after obvious attempts to game the system. *See, e.g.*, Letter from Steven A. Masiello, Dir., Office of Compliance & Biologics Quality, FDA Center for Biologics Evaluation and Research, to Bill Gray, M.D., Bill Gray Med. Corp. (Apr. 2, 2003), http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2003/ucm147405.htm (warning the manufacturer that the product, Dr. Gray's Smallpox Shield, would be regulated as a biologic for containing variolinum which is not listed in the HPUS, as well as for stating that the product required a prescription via a fee-based prescribing service on its website). With regard to the English-labeling requirement, the CPG notes that many homeopathic products bear Latin names that correspond with listings in the HPUS, which mandates Latin names as the primary titles on its monographs. COMPLIANCE POLICY GUIDE, *supra* note 5, at 107; HPUS REVISION SERVICE, *supra* note 66. The CPG goes on to list certain general requirements that homeopathic products are subject to, which are helpful in ensuring that FDA has adequate information and resources to go after a homeopathic drug manufacturer when necessary. These provisions state that all firms that manufacture or otherwise process homeopathic drugs must register as drug establishments and all homeopathic drug products must be listed, consistent with such requirements for drug manufacturer registration and listing in the FDCA and CFR. Similar requirements apply for packaging regulations and current good manufacturing practice regulations. Conversely, the CPG specifically exempts homeopathic products from expiration date regulations. COMPLIANCE POLICY GUIDE, *supra* note 5, at 109.

traditional meaning, not a meaning defined by the law of similars).[89]

Further, consumers who are unfamiliar with the meanings behind homeopathic terms of dilution may not know how much (or how little) of an active ingredient is in a product.[90] Moreover, even many consumers familiar with homeopathy are not aware that many homeopathic OTC drugs do not dilute substances to the extent that traditional homeopathic theory suggests.[91] Thus if labeling fails to clearly reveal the amount of an active ingredient, even those consumers who know that homeopathic drugs are supposed to be highly diluted may be deceived. Zicam is a prime example of this phenomenon: consumers who were familiar with homeopathic theory may not have realized that they were purchasing a product that contained a full 1% of active ingredient—an amount that is surely not infinitesimal.[92]

## III. FUTURE HOMEOPATHIC DRUG REGULATION

Consumer-protection advocates have continually demanded that homeopathic drugs be required to demonstrate safety and efficacy as all other OTC drugs must.[93] Many advocate for this proposal primarily because homeopathic products would likely be eradicated from the market for failure to meet scientific standards.[94] The Zicam incident thus appears

89. *See* ConsumerReportsHealth.org, *supra* note 8 (explaining how consumers might unwittingly buy a homeopathic product without understanding the significant differences between it and an FDA-approved product).

90. *See* NAT'L COUNCIL AGAINST HEALTH FRAUD, *supra* note 14 (complaining that homeopathic labeling only informs consumers about the number of serial dilutions the product has undergone, which does not comport with standard drug labeling that informs consumers of the quantity of active ingredients per dose in known forms of volume measurement, such as milligrams). For the FDA regulations governing nonhomeopathic OTC drug content labeling, see 21 C.F.R. § 201.62 (2009).

91. *See* NAT'L COUNCIL AGAINST HEALTH FRAUD, *supra* note 14 (noting that many homeopathic dosages, although dilute, may contain enough of a substance to affect the body, and asserting that this fact is troubling from a consumer standpoint in light of the lack of proof of safety or effectiveness of homeopathic drugs).

92. *Compare* MedShopExpress, Afrin No Drip Nasal Decongestant Mist, 12 Hour, Original, http://www.medshopexpress.com/586545.html (last visited Apr. 11, 2010) (showing that the active ingredient oxymetazoline hydrochloride in a nonhomeopathic OTC, and thus CFR-compliant, drug is present in a concentration of 0.05% per dose), *with* MedShopExpress, *supra* note 67 (showing that the active ingredient in Zicam nasal swabs was present at a dilution level of 2X, indicating a concentration of 1% per dose).

93. *See, e.g.*, PRAY, *supra* note 22, at 203 (describing a 1994 petition to FDA filed by forty-two health professionals "asking the agency to develop rulemaking procedures to require that all homeopathic drugs be proven safe and effective").

94. *See, e.g.*, NAT'L COUNCIL AGAINST HEALTH FRAUD, *supra* note 14 (recommending that FDA require homeopathic products to meet the efficacy standards of all other drugs); Stephen Barrett, *Homeopathy: The Ultimate Fake*, QUACKWATCH, http://www.quackwatch.org/01QuackeryRelatedTopics/homeo.html (referencing the

to center on FDA's choice of either (1) initiating some form of review to proactively screen homeopathic drugs or (2) continuing with the current regulatory regime, which runs the risk of appearing to disregard FDA's traditional mandate of protecting the public health.[95] Of course protection of the public health is the primary goal of FDA; however, there may be an intermediate path by which to accomplish it in the context of homeopathic drugs.

### *A. Concerns*

First, FDA is an entity of limited resources. Appropriations to the agency have gradually increased over the years,[96] yet many would argue that they have not done so proportionally to the increase in FDA responsibilities. These observations accumulate weight in light of the recent developments at the agency that have accompanied the new Administration. As compared to the noticeable decrease in FDA enforcement actions during the Bush Administration,[97] the Obama Administration FDA has increased its enforcement initiatives.[98] With the recent legislation establishing FDA authority over tobacco products, the agency has also acquired a whole new industry to regulate.[99] These

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author's Freedom of Information Act request that revealed FDA has not found any homeopathic product to be safe and effective, and asserting that if such requirements were finally employed, homeopathic drugs "would face extinction in the United States"—an outcome for which the author strongly advocates).

95. *See* FDCA § 1003(b), 21 U.S.C. § 393(b) (2006 & Supp. 2009) (redesignated from FDCA § 903(b) by Pub. L. No. 111-31, § 101(b)(1), (2), 123 Stat. 1784 (2009)) (setting forth the mission of FDA to protect and promote the public health by effectively monitoring the products it regulates); *cf.* Kevin Gauntt Barker, Comment, *Thank You for Regulating: Why Philip Morris's Embrace of FDA Regulation Helps the Company but Harms the Agency*, 61 ADMIN. L. REV. 197, 221–22 (2009) (maintaining that FDA regulation of tobacco would force the agency to violate its own founding ideology by overseeing a marketed product that is harmful to health and has no offsetting benefit).

96. *See* FDA, Appropriations History Tables, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/2005FDABudgetSummary/ucm112957.htm (last visited Apr. 11, 2010) (charting appropriations for the years 1995–2005, which show a consistent increase each year).

97. *See* SPECIAL INVESTIGATIONS DIV., MINORITY STAFF OF H. COMM. ON GOV'T REFORM, 109TH CONG., PRESCRIPTION FOR HARM: THE DECLINE IN FDA ENFORCEMENT ACTIVITY 1 (2006) (summarizing the report that found a "precipitous drop" in FDA enforcement activities from 2000 to 2005, including instances where FDA headquarters rejected enforcement recommendations of FDA field offices despite serious violations and safety threats found by its officers).

98. *See* Jennifer Corbett Dooren, *Cheerios' Health Claims Break Rules, FDA Says*, WALL ST. J., May 13, 2009, at B1 (noting that the FDA is showing signs of taking a more aggressive stance toward regulated entities under its new leadership, such as the warning letter to General Mills that drew widespread attention).

99. *See generally* Family Smoking Prevention and Tobacco Control Act, Pub. L. No.

developments have resulted in increased appropriations at the request of the President.[100] Yet it remains to be seen how FDA will begin to handle its expanded responsibilities, and any proposal for future homeopathic drug regulation must be viewed within this strained context.

Second, the issue of consumer choice could create significant obstacles to any attempt to increase regulation of homeopathic drugs. FDA battled with the public and inevitably with Congress in its attempts to regulate vitamins and minerals, and subsequently dietary supplements.[101] These products, and all of CAM medicine for that matter, have been shown to be very important to American consumers; the public demands choice.[102] Many argue that the continual consumption of homeopathic drugs by the public is a result of the placebo effect, which could be considered both positive and negative.[103] Yet a significant portion of the population feels that homeopathic drugs truly work, or at least provide refreshing and

111–31, 123 Stat. 1776 (2009) (granting FDA authority to regulate tobacco products "to protect the public health").

100. *See* Press Release, Senate Comm. on Appropriations, Senate Approves FY 2010 Agriculture, Rural Development and FDA Appropriations (Aug. 4, 2009), http://appropriations.senate.gov/news.cfm?method=news.view&id=fc50e8f8-5a35-4349-876a-ab83515a7de9 (announcing that FDA will receive $299 million above the amount allocated to the agency for fiscal year 2009).

101. *See generally* PRAY, *supra* note 22, at 205–17 (providing a history of dietary supplement regulation, including the extensive back-and-forth struggle between FDA and Congress resulting in three separate statutory amendments, in which the entities had starkly opposing views as to how restrictive an approach the agency should take with regard to dietary supplements).

102. *See, e.g.*, Draft Guidance for Industry on Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration, 72 Fed. Reg. 29,337, 29,338 (May 25, 2007) (stating that FDA had received such a large volume of comments that it was unable to identify and respond to extension requests, and clarifying that the outcry was a result of "misinterpretation"; to calm it, FDA made clear that it did not propose any new regulatory requirements for CAM products, licensing of CAM practitioners, or consumer ability to purchase CAM products or be treated by a CAM practitioner)*; see also* Kathleen M. Boozang, *National Policy on CAM: The White House Commission Report*, 31 J.L. MED. & ETHICS 251, 251 (2003) (examining the White House Commission on Complementary and Alternative Medicine policy, which was established by President Clinton in 2000 to maximize the benefits of CAM in America as a response to consumers "voting with their health care dollars").

103. For an explanation of the placebo effect—the psychological phenomenon of patients purportedly recovering from various conditions when they think they are taking a new drug, but are actually receiving a placebo—see Tamar Nordenberg, *The Healing Power of Placebos*, FDA CONSUMER, Jan.–Feb. 2000, at 14, 14–17. For a critical view that analyzes the beneficial claims made by placebo proponents, see Harriet Hall, *The Placebo Effect*, 15 SKEPTIC 56 (2009), and Stephen Barrett, *Spontaneous Remission and the Placebo Effect*, QUACKWATCH, http://www.quackwatch.org/04ConsumerEducation/placebo.html. For information on the 1955 groundbreaking medical study on the placebo effect, see Henry K. Beecher, *The Powerful Placebo*, 159 JAMA 1602 (1955).

hopeful alternatives to conventional medicines.[104] Congress has done what it can to enable consumer choice in this forum,[105] thus any attempt by FDA to limit it could be seen as a contravention of congressional intent. This may or may not provoke congressional action rendering stricter FDA regulation moot.

Third, there are the issues of safety and consumer protection. Critics will be quick to point out that consumers cannot be exercising a meaningful choice when they do not know what they are choosing.[106] If consumers are unaware of the premises behind homeopathy, or if they are unaware of the differences in regulatory oversight between homeopathic and traditional OTC drugs, they are not only being misled, but they could be unknowingly subjecting themselves to harm. This harm could be the result of substituting homeopathic drugs for products that have been proven effective or of taking an uninformed risk on a product that has not been tested for safety. Ultimately, consumers cannot protect themselves from a product that not even FDA knows is unsafe when it enters the market—case in point: Zicam.

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104. *See* Lawrence J. Schneiderman, *The (Alternative) Medicalization of Life*, 31 J.L. MED. & ETHICS 191, 195 (2003) (recounting a survey conducted by the author and one of his medical students which consisted of interviewing 100 people in San Francisco who were consulting homeopathic practitioners—he states that these "were not unsophisticated people who were unaware of modern medicine" but rather highly educated people with chronic and painful conditions, such as chronic asthma and chronic arthritis, who were seeking treatment outside scientific medicine which "did not give them the cure they were hoping for"); *The Role of Early Detection and Complementary and Alternative Medicine in Women's Cancers: Hearing Before the H. Comm. on Government Reform*, 106th Cong. 8 (1999) (opening statement of Rep. Dan Burton, Chairman, H. Comm. on Government Reform) (orating the committee's goal to "break through barriers of institutional bias" against complementary and alternative therapies for cancer in an effort to improve the availability of information and treatment options to citizens suffering from the disease).

105. *See, e.g.*, *Alternative Medicines: Hearing Before the Subcomm. on Labor, Health, and Human Servs., and Education, and Related Agencies of the S. Comm. on Appropriations*, *supra* note 32, at 2–3 (opening statement of Sen. Tom Harkin, Member, Subcomm. on Labor, Health, and Human Servs., and Education, and Related Agencies of the S. Comm. on Appropriations) (touting the benefits of CAM and describing efforts, including the establishment of NCCAM within NIH and the grant of funding to the White House Commission on Complementary and Alternative Medicine, to enable the public to access such treatments). *But see* Bridget M. Kuehn, *Despite Health Claims by Manufacturers, Little Oversight for Homeopathic Products*, 302 JAMA 1631, 1631 (2009) (reporting that clinical trials on CAM products have been hampered in the homeopathic context due to many trials on such products containing methodological flaws, such as not having an appropriate placebo control, resulting in proposals to NCCAM being necessarily rejected for funding).

106. *See* NAT'L COUNCIL AGAINST HEALTH FRAUD, *supra* note 14 (accusing drug manufacturers of labeling their products as homeopathic in order to evade regulation, resulting in an "explosion" of such products in recent years that consumers do not fully understand).

### *B. A Homeopathic OTC Drug Review?*

If FDA finally followed through with its 1972 promise to subject homeopathic OTC products to a separate official drug review, it would face many of the same problems that it did in 1972.[107] In addition to limited resources and complicated logistics, the largest problem facing a full review of OTC homeopathic drugs is the efficacy issue. The HPUS states, "Because homeopathic drug provings are pharmacological studies on healthy volunteers, they are quite similar to Phase I clinical trials."[108] Examination of this deceptively vague statement reveals the incompatibility of the HPUS with the standards articulated by FDA, and thus the futility of a homeopathic drug efficacy review.

First, although FDA-mandated Phase I studies on conventional drugs are performed on healthy volunteers, they mainly focus on discerning the initial safety picture of the drug and the exact pharmacological effect of the drug on the human body.[109] They are a very preliminary step in the long path to FDA drug approval, as a drug's NDA approval will generally be conditioned on documentation of several subsequent controlled clinical trials definitively proving a positive risk–benefit ratio between the safety and effectiveness of the drug.[110] Conversely, a single homeopathic proving satisfies the evidentiary standards of the HPUS.[111] Provings are

107. *See supra* notes 59–60 and accompanying text.

108. HPUS REVISION SERVICE, *supra* note 66.

109. *See* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 630 (excerpting from a FDA Center for Drug Evaluation and Research handbook that describes the purposes of Phase 1 trials on investigational new drugs, which include, as a purely secondary measure, the gathering of early evidence of effectiveness "if possible").

110. *See generally* 21 C.F.R. § 314.50 (2009) (setting forth the required content of an NDA, including information on chemistry and pharmacology of the drug, animal studies, multiple human studies, and patent information); Gary L. Yingling & Ann M. Begley, *Clinical Research Requirements for New Drug Applications*, *in* THE PHARMACEUTICAL REGULATORY PROCESS, *supra* note 40, at 199–212 (describing the three phases of clinical studies—phase one: toxicology; phase two: dose range; and phase three: efficacy—and detailing the many compliance considerations that must be taken into account during this testing, including sponsor submission requirements, clinical investigator oversight, institutional review board approval, and proper record keeping and reporting to FDA). Prescription-to-OTC switching and approval of generic medications do not require the extensive testing mandatory for NDA submissions; however, these processes occur subsequent to NDA approval of a drug which has thus already satisfied safety and efficacy requirements. *See generally* PRAY, *supra* note 22, at 180–81 (discussing methods by which approved prescription drugs can be switched to OTC and showing that "new" OTC drugs generally arrive on the OTC market by first satisfying NDA requirements to be sold as prescription drugs and later switching to OTC); Marc S. Gross et al., *Generic Drug Approval Process: Hatch-Waxman Update*, *in* THE PHARMACEUTICAL REGULATORY PROCESS, *supra* note 40, at 61 (detailing the Drug Price Competition and Patent Term Restoration Act, or Hatch–Waxman Act, of 1984, which established the current generic drug regime).

111. *See* HPUS REVISION SERVICE, *supra* note 66 (listing the documents required for

administrations of substances to healthy persons to observe what symptoms are produced, and thus what symptoms the substance can potentially treat. Notably, this process fails to test the actual product on people experiencing those symptoms. This fact flies in the face of FDA's traditional clinical trial requirements.[112]

Second, the HPUS does not list the symptoms that a substance produced in a proving. HPUS monographs list only descriptive elements of active ingredients, details on drug preparations, and the lowest potency at which a product may be sold for OTC use; they therefore do not clearly correlate drugs with their effect on the body, which would be necessary for any traditional FDA efficacy determination.[113] In comparison, a United States Pharmacopeia (USP) monograph for an active drug ingredient features a detailed description of a chemical assay that produces the pharmacological effect of the drug in the human body.[114] Additionally, each OTC drug monograph in the CFR states the specific conditions to be treated by each active ingredient, which are thus permitted on the labeling of products containing approved active ingredients because the ingredients have been clinically proven safe and effective for use with such conditions.[115] FDA's

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acceptance of a homeopathic remedy into the HPUS, which include (1) documents showing the qualification of the principal investigator, which must show that he or she has been a homeopathic drug prescriber for five years and have at least two years' experience in drug provings; (2) the proving protocol, which "should be carried out according to Hahnemann's classical directions" as stated in his ORGANON OF HOMEOPATHIC MEDICINE (North American Academy of the Homeopathic Healing Art eds., 1836); and (3) the final report of the homeopathic drug proving, which must include, among other things, a compilation and classification of the symptoms observed and evaluated).

112. *See* 21 C.F.R. § 314.126(b)(2) (2009) (listing requisite elements of an "adequate and well-controlled" study, one element of which is a study design "that permits a valid comparison with a control to provide a quantitative assessment of drug effect," i.e., to evaluate if the drug has the effect it is supposed to have). The HPUS states that other research methods may be considered for clinical verification and potential inclusion in the HPUS, in an acknowledgement "that a range of methods are currently being used in homeopathic drug provings." HPUS REVISION SERVICE, *supra* note 66. Such methods include "case series, outcome studies, prospective observational studies, longitudinal data collection networks, or randomized controlled trials." *Id.* Although such alternative testing may provide more insight into traditional effectiveness information on homeopathic drugs, it does not shift the premise of homeopathic drugs, and thus the efficacy analysis, away from the law of similars.

113. HPUS REVISION SERVICE, *supra* note 66; *supra* note 110 and accompanying text.

114. *See, e.g.*, COMM. OF REVISION, U.S. PHARMACOPEIAL CONVENTION, INC., USP XXII, at 12–13 (1990) (featuring the assay for acetaminophen). Some HPUS monographs feature an assay for accurate preparation of the monograph ingredient; however, the proven pharmacological effect associated with USP assays is absent in HPUS assays due to the reliance of the HPUS on the law of similars.

115. *See, e.g.*, 21 C.F.R. § 341.20 (2008) (listing nasal decongestant active ingredients approved for OTC marketing, such as pseudoephedrine hydrochloride); *id.* § 341.80 (setting forth the precise mandatory labeling for nasal decongestant OTC drugs, including a

governing CPG does refer industry personnel to two century-old books that provide information on the relationship of homeopathic drugs to symptoms and indications for use.[116] The texts, however, are far from comparable to modern scientific proof of efficacy. It is thus unclear how FDA would designate a definitive endpoint for homeopathic drug efficacy testing—it could surely look to homeopathic publications and individual product claims to determine what conditions a drug is supposed to treat, and thus what indications to test for; however, the clinical uncertainty accompanying these sources, evidenced by their reliance on the law of similars, would make any study highly questionable and likely futile.

In considering the option of a homeopathic OTC drug review, one cannot escape the efficacy issue, which has been around since homeopathy's inception. If FDA decided to confront it, the agency would be endorsing the end of homeopathic OTC drugs—few if any could satisfy current efficacy standards, and for this reason even fewer manufacturers would be willing to expend the time and money necessary to prove otherwise. This fact advises against a full homeopathic OTC drug review if homeopathic drugs are to remain on the market as an option for the consuming public. Unlike the efficacy issue, however, the occurrence of serious adverse events associated with homeopathic drugs renders the safety issue a new and very important concern that FDA would be remiss to ignore.[117] A limited homeopathic OTC drug review is warranted to ensure the safety of such products in light of new safety information exposed by the Zicam incident.[118] The modern drug market, which features Internet

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requirement for a stated indication of temporary relief from nasal decongestion).

116. *See* COMPLIANCE POLICY GUIDE, *supra* note 5, at 107 (stating that John Henry Clarke, M.D.'s volumes on homeopathic drugs, *A Dictionary of Practical Materia Medica* (1902) and the concomitant *A Clinical Repertory to the Dictionary of Materia Medica* (1904), should be reviewed along with other available information by agency personnel in order better understand homeopathic drugs).

117. One potentially positive aspect of the HPUS is that drug provings can be inherent safety tests—by administering substances in larger doses than will be administered in the final diluted products, they can ensure a certain margin of safety. However the HPUS itself states that provings require an alteration of the definition of *adverse event* in the homeopathic context to reflect the fact that all side effects are recorded for purposes of determining how the drug will be used, not what the drug labeling should warn against. HPUS REVISION SERVICE, *supra* note 66. Accordingly, the safety issue remains uncertain.

118. An argument against this approach may point out the existence of other drug safety measures at FDA's disposal. FDA currently houses an adverse event reporting program called MedWatch on the FDA website. FDA, MedWatch: The FDA Safety Information and Adverse Event Reporting Program, http://www.fda.gov/Safety/MedWatch/default.htm (last visited Apr. 11, 2010). The agency is also in the process of implementing a new comprehensive safety data network, titled the Sentinel Initiative, which will pull data from several sources to supply a one-stop-shop for comprehensive adverse event and drug safety information. OFFICE OF CRITICAL

pharmacies, pervasive advertising, and growing expenditures on health care, highlights the potential regulatory and public health implications associated with homeopathic OTC drugs. With a view to FDA priorities, which have traditionally followed a risk-based enforcement approach,[119] the safety issue associated with these products outweighs the efficacy issue, leading to the need to address only homeopathic OTC drug safety in the context of limited FDA resources.[120]

### *C. The Safety Issue: A Limited Homeopathic OTC Drug Safety Review*

When FDA initiated the gargantuan undertaking of the OTC Drug Review, it came up with the novel approach of establishing advisory review panels comprised of experts specially qualified to evaluate distinct

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PATH PROGRAMS, FDA, THE SENTINEL INITIATIVE: NATIONAL STRATEGY FOR MONITORING MEDICAL PRODUCT SAFETY 13 (2008) http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf. FDA's power over postmarket drug safety was also greatly increased by the Food and Drug Administration Amendments Act of 2007, under which FDA may now require postmarket studies and clinical trials upon discovery of new safety information (i.e., upon new adverse experiences with a drug). FDCA § 505(o)(3)(A)–(B), 21 U.S.C. § 355(o)(3)(A)–(B) (Supp. I 2007). These safety measures, however, were established to monitor drugs that have already undergone traditional safety and efficacy testing. They are additional reactive measures—undertaken after the proactive FDA review and approval process—which are intended to address adverse events that can only emerge when a drug is released for widespread use by the public. Homeopathic drugs, in contrast, are currently subject only to the reactive approach exemplified by the Matrixx warning letter, such drugs having never been subject to any form of premarket safety review that would indicate potential side effects.

119. *See generally* FDA, COMPLIANCE POLICY GUIDES § 440.100, MARKETED NEW DRUGS WITHOUT APPROVED NDAS AND ANDAS (2006), *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm (outlining how FDA will exercise its enforcement discretion with regard to drugs marketed illegally for failure to obtain required FDA premarket approval). The enforcement priorities of this CPG primarily focus on unapproved marketed drugs that pose safety threats, consistent with FDA's foremost mission of protecting the public health. Leaving the unique situation of homeopathic drugs aside, the policies of this CPG are indicative of FDA's general enforcement approach.

120. *But see generally id.* (discussing the priority of enforcement against both ineffective drugs and health fraud drugs which are likely to pose "indirect health hazards" if the consumer is likely to delay or discontinue appropriate medical treatment in reliance on the drug). Although the health fraud focus of this CPG brings the efficacy issue to the fore, it does not follow that homeopathic drug efficacy should be the primary focus of FDA's attention in regulating homeopathic drugs. The homeopathic CPG addresses health fraud, and in doing so, it indicates that ineffective homeopathic drugs deemed to pose serious indirect health risks will not be overlooked under the dual coverage of the homeopathic CPG and FDA's health fraud regime. *See, e.g.*, United States v. Writers & Research, Inc., 113 F.3d 8, 10–11 (2d Cir. 1997) (upholding FDA's seizure of homeopathic drugs claiming to cure life-threatening diseases). The homeopathic drugs at issue in this case can be characterized as classic serious health fraud drugs for claiming a false curative value which, if relied on, posed the threat of imminent fatality.

therapeutic categories of OTC drugs.[121] The panels evaluated data that came from OTC drug makers, other interested parties, and the available scientific literature to determine safety and effectiveness of an active ingredient for its intended use.[122] In light of the preceding efficacy discussion, the OTC Drug Review model would require alteration to fit the homeopathic context. However, it is a valuable tool with which to approach the task.

The HPUS specifies the minimum dilution—i.e., the highest concentration—at which each listed ingredient can be sold OTC. Although seemingly an adequate safety barrier, the last update of these standards was in 1998,[123] and the Zicam incident has exposed areas that create a cause for concern. Specifically, the HPUS specifies the minimum dilution at which each drug can be sold for "external use," which is defined as application to the eyes, ears, nose, or other bodily surface other than the mouth or other bodily orifice.[124] Minimum dilutions for external use are generally lower than minimum dilutions for general OTC use—i.e., drugs made for topical application can be sold with higher concentrations of active ingredient than drugs intended for ingestion. For example, the HPUS sets the minimum OTC dilution for "zincum gluconium" at 1X, for "zincum bromatum" at 3X, and for "zincum muriaticum" at 6X; however, the minimum external use dilution for all three of these ingredients is listed as "N/A."[125] The HPUS explains that these standards were developed

121. *See* PRAY, *supra* note 22, at 174–75 (discussing the panels and noting that although prior experience with the DESI Review of prescription drugs greatly aided FDA, the task was still "one of the most ambitious and comprehensive programs ever undertaken by the agency"); *see also* 21 C.F.R. § 330.10(a)(1) (2009) (explaining the advisory panel review system).

122. *See* PRAY, *supra* note 22, at 176 (setting out the criteria the panels used to analyze all the relevant data, including the existence of any clinical trials, the development of scientific opinion on the ingredient, and the marketing experience of the OTC drugs, including sales volume and the amount of complaints received); *see also* 21 C.F.R. § 330.10(a)(2) (2009) (setting forth the process by which FDA would request data via publication in the *Federal Register*; all "interested persons" were asked to submit pertinent materials); *id.* § 330.10(a)(4) (stating the safety and efficacy showing requirements of the review).

123. HPUS REVISION SERVICE, *supra* note 66.

124. *Id.* The HPUS also states lower dilutions at which a drug can be sold by prescription. Although lower dilutions inherently implicate greater safety concerns, homeopathic prescriptions should be an ancillary concern for FDA because they are monitored by a licensed practitioner. As previously mentioned, this Comment's discussion pertains strictly to homeopathic OTC products in recognition of the many additional considerations accompanying the issue of homeopathic practitioners, such as licensing, standard of care, reimbursement, and medical integration. For a discussion on these issues, see generally Cohen, *A Fixed Star*, *supra* note 44.

125. HPUS REVISION SERVICE, *supra* note 66.

using "acute toxicity data from the literature."[126] Thus, despite a stated literature examination by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS), the HPUS featured no limit as to the level of zinc concentration that Matrixx could use in its Zicam intranasal zinc products. This is alarming considering that risk indicators linking intranasal zinc application to anosmia have been around for decades in the literature and in practice.[127] The HPUS further states that the minimum dilution levels were determined within a "100-fold margin of safety" based on accidental ingestion by a 10-kilogram (approximately 22-pound) child of an average amount of ingredient in a full drug container, 30 milliliters or 16.2 grams.[128] This methodology seems to ignore external use entirely, despite the knowledge that the term *external use* includes sensitive bodily areas.

In light of the seriousness of the Zicam incident and the shortcomings that it has revealed, FDA action is warranted. The most efficient proposal is for a very limited safety review to evaluate the scientific literature on homeopathic drug ingredients and ensure that the HPUS minimum dilutions do in fact render homeopathic OTC drugs safe under FDA standards. To accomplish this, FDA should follow the OTC Drug Review model to establish an advisory review panel comprised of homeopathic, herbal, and chemical experts that are qualified to evaluate relevant information on each ingredient featured in the HPUS. As with the OTC Drug Review, FDA can issue a call for data submissions, which will enable manufacturers to show safe public experience with a particular ingredient if possible. There are 1,286 monographs in the HPUS, and in comparison to the OTC Drug Review that examined approximately 200 active ingredients, this number may appear daunting. However, a limited homeopathic safety review would only require evaluation for safety, not efficacy for intended uses; unlike the panels of the OTC Drug Review, the homeopathic drug safety panel would not be responsible for drafting

126. *Id.*

127. *See* Warning Letter, *supra* note 2 (acknowledging existing evidence "in the published scientific literature" linking zinc to olfactory damage); Kuehn, *supra* note 105, at 1632 (citing the existence of case studies in the medical literature of anosmina in patients that used zinc intranasally, as well as historical information on how the intranasal use of zinc in an attempt to prevent polio in the 1930s was linked to anosmia); Jablow, *supra* note 1, at 78–80 (describing the failed polio vaccine that resulted in anosmia as well as a more recent University of Colorado Study that concluded there was a direct link between nasal exposure to zinc and olfactory receptor cell damage); *see also supra* Part II.A (discussing Matrixx's inability to claim safety of its intranasal zinc products despite the general safety of oral zinc products in light of published literature showing zinc to cause olfactory harm).

128. HPUS REVISION SERVICE, *supra* note 66.

monographs with detailed labeling and warning requirements.[129] Further, the nature of homeopathic ingredients will render them much easier to review—a long history of safe experience will cover many herb and mineral ingredients, and some ingredients are used in vitamins and dietary supplements, for which abundant safety data should be available.[130] The panel should be responsible only for determining the potencies at which homeopathic ingredients can be safely marketed without going through more thorough testing for full NDA approval. With the aid of the HPCUS and the cooperation of the industry, this should not be a burdensome review. FDA can also considerably preserve resources by addressing the new safety policy through a new CPG instead of promulgating regulations—compliance with FDA minimum dilution standards can be another condition under which homeopathic products may be marketed.[131]

Incorporating a limited safety review into FDA's homeopathic drug regime would likely assuage public concern about homeopathic drug oversight and safety by ensuring more congruence with the existing OTC drug regime that was precipitated by the OTC Drug Review advisory panel approach. Additionally, limiting the review to a discrete safety purpose would be congruent with FDA's risk-based priorities. Ultimately, the benefit of such an approach would be to recognize the potential for

129. FDA's overarching standard in approving a new drug has historically been a determination that the benefits of the drug outweigh its risks. *See* HUTT, MERRILL & GROSSMAN, *supra* note 40, at 694–95 (discussing FDA's choice to employ an integrative approach to the FDCA requirements for safety and efficacy, which textually can be read as independently satisfied standards). The concept of efficacy is inherent in a consideration of benefits; therefore, FDA's analysis is essentially a weighing of efficacy versus safety, with the many detailed considerations such an analysis entails. However, because the current CPG provisionally exempts homeopathic drugs from the FDCA safety and efficacy requirements, homeopathic drugs are not subject to the benefit–risk standard, leaving FDA free to shape a different standard. It appears from the Zicam incident that FDA has already formulated a threshold at which it considers a homeopathic drug too dangerous to be marketed OTC. Thus, FDA can likely utilize existing criteria to set forth a concrete standard of review.

130. *See, e.g.*, HPUS REVISION SERVICE, *supra* note 66 (featuring the monograph for caffeine).

131. The main drawback to this approach is the fact that compliance policy guides are just that—policy guides, not rules that carry the force of law. *See generally* Stephen M. Johnson, *Good Guidance, Good Grief!*, 72 MO. L. REV. 695 (2007) (addressing the use of interpretive policy documents by agencies to create binding rules outside of the notice-and-comment process prescribed in the Administrative Procedure Act—one complaint against this method is the uncertainty surrounding the vitality of such policy documents created by conflicting opinions on the degree of judicial deference owed to them). However, considering the facts that the current homeopathic drug regime is anchored in a CPG, and that FDA has historically been able to utilize its enforcement discretion to obtain compliance with the policies enumerated therein, continuing with the CPG approach for any new safety criteria coming out of the homeopathic drug advisory panel review is likely the most efficient approach.

harm and prevent it—surely such a review would have prevented hundreds of unknowing consumers from using Zicam intranasal products and temporarily or permanently losing their sense of smell.

### *D. The Consumer Protection Issue: New Homeopathic OTC Drug Labeling Requirements*

In the Dietary Supplement Health and Education Act of 1994 (DSHEA), Congress allowed dietary supplement manufacturers to make labeling claims indicating a supplement's effect on the structure or function of the body, under the condition that the claims be substantiated.[132] The claims must also be accompanied by a disclaimer that states, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."[133] The regulatory regimes governing dietary supplements and homeopathic drugs are divergent, and should be, in recognition of the differing conceptions behind the products—unlike dietary supplements, homeopathic drugs are very much intended to diagnose, treat, cure, or prevent disease. Nevertheless, although the dietary supplement regime may not be applicable in the homeopathic drug context, the labeling approach that Congress took in DSHEA is valuable in considering revised labeling requirements for homeopathic products.

The policy behind DSHEA was to facilitate consumer access to safe dietary supplements.[134] The legislation encouraged dissemination of truthful information regarding such products in the form of structure and function effectiveness claims, which FDA had previously disallowed.[135] Although most homeopathic drug claims are different from the claims

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132. *See* FDCA § 403(r)(6), 21 U.S.C. § 343(r)(6) (2006) (delineating the types of structure and function claims manufacturers may make regarding dietary supplements and the conditions under which such claims will not render the products misbranded); *see also* FDCA § 201(g)(1)(D), 21 U.S.C. § 321(g)(1)(D) (2006) (stating that a dietary supplement does not become a drug if it makes a claim in accordance with the FDCA provisions regulating such claims).

133. FDCA § 403(r)(6)(C), 21 U.S.C. § 343(r)(6)(C) (2006).

134. *See* Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 2(13), 108 Stat. 4325, 4325–26 (1994) (stating congressional intent not to impose unreasonable regulatory barriers on the flow of safe dietary supplements and accurate information regarding their benefits to consumers).

135. *See id.* § 2(5) (touting the societal benefits to be gained from promotion of education regarding good nutrition and safe use of nutritional supplements); PRAY, *supra* note 22, at 212–16 (discussing the two prior pieces of legislation in 1990 and 1992 in which Congress attempted to loosen FDA's restrictions on dietary supplement claims, and the 1994 legislation, DSHEA, which finally succeeded). Senator Orrin Hatch, the driving force behind DSHEA, stated that FDA's "single-minded" approach forced Congress to intervene. *Id.* at 216.

allowed by DSHEA, the congressional method of ensuring that the public did not take away the wrong message from the claims—the required disclaimer—can be utilized for the same purpose with homeopathic OTC drugs. To alert consumers to the truthful scientific and regulatory posture of homeopathic OTC drugs, FDA should require a labeling statement indicating that FDA has not evaluated the effectiveness of the product for its intended use. In addition, to ensure that consumers know the precise contents of a drug, FDA should require that homeopathic OTC drug labeling reflect the amount of active ingredient in traditional units of measurement and percentage next to the homeopathic dilution level. This latter requirement will enable consumers who are not familiar with homeopathic theory to understand exactly what they are purchasing—if a product features such a small percentage of an active ingredient as to render it essentially nonexistent, this labeling requirement will let consumers know. Concomitantly, it will apprise consumers who may be expecting a very high dilution from a homeopathic product if a drug is actually much less diluted (i.e., more potent) than traditional homeopathic theory would suggest. Akin to the policy behind DSHEA of enabling access while promoting informed purchasing, such an approach would sufficiently apprise consumers of necessary purchasing information that is currently lacking in homeopathic OTC drugs.

This approach has the advantage of not only preserving consumer choice but also promoting a more meaningful choice by providing consumers with the details necessary to make an informed decision. To implement the new labeling requirements, FDA can again utilize the CPG approach.[136] Although the homeopathic regulatory framework would continue to be a more attractive option than the traditional drug regime for manufacturers who deliberately seek to avoid efficacy requirements, informative labeling will at least decrease instances of mistaken purchases of such products. Moreover, by utilizing labeling as a vehicle for preserving consumer choice, FDA would have the benefit of following the lead of Congress who implemented the method with regard to dietary supplements. This could create a potential safe harbor for FDA's new homeopathic OTC drug regime.

## CONCLUSION

The governing CPG listing conditions under which homeopathic drugs may be marketed was released over twenty years ago at the brink of the Internet age and the early stage of growth in CAM popularity among the

136. FDA already prescribes its homeopathic drug labeling requirements via the governing CPG. *See supra* Part II.C; COMPLIANCE POLICY GUIDE, *supra* note 5, at 107–09.

American consuming public. Not only have these phenomena proven to be much more than passing trends, but traditional concepts of information dissemination and product availability have greatly expanded along with them. The Zicam incident brings to the fore FDA's insufficient oversight of homeopathic drugs and raises concern over the potential effects of such a lax approach in modern society. FDA can make the choice to continue with the reactive enforcement scheme of its current CPG despite changing conditions, which may be a valid resource-conserving approach. However, in light of the heightened public scrutiny raised by the Zicam incident and a new Administration that is clearly encouraging FDA to meaningfully fulfill its mission, now may be the best time to reexamine the homeopathic drug regulatory regime and shape it to reflect modern expectations of safety and information in medical choices.