

Comment on FDA Draft Guidance for Staff and Industry: *Drug Products Labeled as Homeopathic*. 82 Fed. Reg. 60403 (proposed Dec. 20, 2017)

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I. Introduction

A. Who We Are

The Duke Science Regulation Lab is a group of graduate students across multiple disciplines at Duke University including bioethics, law, the sciences, and global health. The ultimate goal of this group is to bring together individuals from diverse academic backgrounds to submit comments to proposed rules dealing with scientific issues. The Science Regulation Lab was originally inspired by the traditional role of *amicus curiae*: to provide a court with the unbiased information necessary to reach a binding decision. As an extension of that concept, we now provide government agencies with the scientific information necessary to undertake effective rulemaking.

Modern society requires our government to handle increasingly complex scientific issues when deciding cases or making policy. The members of the Science Regulation Lab believe the public benefits from judgments based on sound scientific knowledge. Providing accurate and unbiased comments on proposed rules and regulations will help facilitate this process by informing policy makers about the relevant science.

The authors are members of the Science Regulation Lab with a range of academic disciplines. **Kirsten Bleiweiss** is a first-year student in the Master of Arts in Bioethics & Science Policy program, with an academic focus on neuroscience and the law. **Yoonah Lee** is a 2018 Juris Doctor Candidate focusing on intellectual property litigation. **Marcia K. Lindsey** is a first-year student in the Master of Arts in Bioethics & Science Policy program, with an academic focus on regulatory law and public policy. **Melissa Morales** is a first-year student in the Master of Arts in Bioethics & Science Policy program, with an academic focus on the regulation of emerging technologies. **Brendan Neville** is a 2018 Juris Doctor Candidate with a focus on criminal and civil litigation. **Sarah E. Philo** is a second-year student in the Master of Science in Global Health program. Her research focuses on emerging infectious diseases.

¹ The authors are all graduate students in the Duke Science Regulation (SciReg Lab), an interdisciplinary course offered through the Duke Law and Graduate Schools. Pate Skene and Michael B. Waitzkin are the faculty members who run the SciReg Lab and oversaw the preparation of this Comment.

B. FDA Draft Guidance on Drugs Labeled as Homeopathic

The Food and Drug Administration (FDA) published a request for comment on their draft guidance prioritizing the order in which they plan to enforce and regulate drugs currently labeled as homeopathic. Simultaneously with this draft guidance, the FDA is withdrawing Compliance Policy 400.400, Conditions Under Which Homeopathic Drugs May be Marketed [1]. FDA new drug applications require both prescription and over-the-counter (OTC) drug manufacturers provide evidence of safety and efficacy [1]. However, homeopathic drugs have not historically been required to obtain this FDA approval [1]. Therefore, they may pose a public health threat because they have not been shown to meet FDA safety, efficacy, quality, and labeling requirements [1].

The FDA began to reevaluate the existing structures around homeopathic medicines in 2015. In April 2015 they held a public hearing seeking input from stakeholders about the current use of homeopathic drugs and the regulatory framework surrounding homeopathic drugs [2, 3]. Following this public hearing, the FDA concluded a risk-based approach for prioritizing enforcement and regulation of homeopathic drugs would be most effective and remain consistent with other FDA regulatory frameworks [3].

In the proposed guidance, the FDA identifies six areas to prioritize regulation of homeopathic drugs:

- Products with reported safety concerns.
- Products that contain or purport to contain ingredients associated with potentially significant safety concerns.
- Products for routes of administration other than oral and topical.
- Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions.
- Products for vulnerable populations.
- Products deemed adulterated under section 501 of the FD&C Act.

The FDA has requested comments on their proposed risk-based guidance. We support the FDA's regulatory proposal and find the risk-based approach appropriate given the history of homeopathic drugs. Additionally, we agree with the FDA that their proposed factors reflect some of the relevant risks. However, we argue the FDA has left out a significant factor in that they do not consider the users of homeopathic drugs and risks associated with those populations. Important for understanding the user-risks of homeopathic medicine are including prioritization of social determinants of health (SDH).

In this comment, we will first outline our agreement with the FDA on the need for new guidance. Next, we will discuss whether or not the proposed guidance will appropriately address the public health risks of homeopathic medicine and whether or not the factors are the correct way to conduct risk-based enforcement. We will finish our comment by suggesting the FDA also consider socially vulnerable populations and provide demographic data on the users of homeopathic medicine. We will point out problems with the available data and provide suggestions about how to order the proposed enforcement factors. We support the FDA's movement for guidance of homeopathic drugs, but we propose they also consider SDH in their proposed prioritization of vulnerable populations.

II. Need for FDA Regulation of Homeopathic Drugs

Considering the history of homeopathic medicine, existing regulations, and recent developments of homeopathy, new risk-based guidance is timely and appropriate. The current regulation in place for homeopathic drugs is limited and calls for additional guidance. In particular, current regulation fails to address two potential concerns: direct harm arising from toxicity of the drugs and indirect harm arising from preventing and delaying proper treatment due to the consumer belief that the label “homeopathic” means the drug is safe and effective [4]. Prevalence of homeopathic use has expanded recently, therefore it is essential to address safety concerns. The recent expansion of homeopathic product use also, in combination with the historical development of homeopathic medicine, supports the need for additional guidance.

A. History

Homeopathy was founded by a German physician Samuel Hahnemann in response to conventional medicine, which he believed caused more harm than good [5]. While translating books on medicine, agriculture, and chemistry, he developed the principle of the law of similars [5]. This principle is fundamental to homeopathy and aims to “let like cure like” [5]. In other words, drugs inducing symptoms will in effect cure the individual from those symptoms [5]. Another key principle of homeopathy—the law of infinitesimals—concerns the amount, or dosage, of the substance [6]. The law of infinitesimals suggests drugs’ effects are more powerful in highly diluted form [6]. Together, these two fundamental homeopathic principles indicate homeopathic drugs are meant to treat an illness with a diluted form of a substance that causes symptoms of the illness [6]. Because non-diluted homeopathic drugs cause adverse outcomes, there are inherent risks of homeopathic treatments. This inherent risk raises concerns about the need to demonstrate safety and efficacy.

In homeopathy, drugs are tested using a distinct process called proving [5]. In proving, remedies are given to healthy persons in order to test the physical and emotional effects of the remedy [5]. However, there is a paucity of formalized clinical trials to ensure the safety and efficacy of homeopathic treatments [7]. The FDA has issued warnings in the past because some homeopathic treatments are associated with loss of the sense of smell, seizures, and even death [8]. In fact, systematic reviews from 2012 and 2016 suggest homeopathic drugs’ adverse effects result directly from their toxicity [9, 10]. Although there have been attempts to regulate homeopathic treatments, potential adverse effects have not been directly addressed in these regulations [7].

Because there are few regulations surrounding the safety of homeopathic treatments, in 1988 the FDA attempted to set some standards for homeopathic drugs. In consultation with the American Association of Homeopathic Pharmacists (AAHP), the FDA issued the Compliance Policy Guide 400.400 (CPG), *Conditions Under Which Homeopathic Drugs May Be Marketed*, to create guidelines for the manufacturing and marketing of homeopathic products [11]. Although the guidelines improved the standard of homeopathic products and helped eliminate counterfeits, they do not address potential adverse outcomes of homeopathic treatments [11].

B. Existing Regulations

Homeopathic drugs are currently regulated by the Homeopathic Pharmacopoeia of the United States (HPUS). While the FDA retains overarching authority to regulate homeopathic drug products, the HPUS has traditionally created industry standards and guidelines for homeopathic substances. The HPUS maintains a list of active ingredients in a modern *materia medica*; four volumes consisting of around 1,300 individual drug monographs and the general pharmacy referred to as the Homeopathic Pharmacopoeia of the United States Revision Service (hereinafter the Revision Service) [12].

The first component of the Revision Service, the general pharmacy, consists of the manufacturing methods for official homeopathic drugs and standardization guidelines. The Revision Service guidelines considers safety, efficacy, and standardization in production methods [13]. These three factors are set using the method ‘proving’ rather than FDA standards for non-homeopathic drug products [13]. While a subscription service allows access to the database, the standards and guidelines related to safety claims are not publicly available. Therefore, the consumer may have trouble learning about homeopathic products given the lack of accessible information.

The second component of the Revision Service are the individual drug monographs. The monographs list identifying data and manufacturing standards for each recognized homeopathic drug [12]. The CPG allows both OTC and prescription (Rx) homeopathic drug products to be marketed and sold. The HPUS differentiates between official and nonofficial homeopathic drugs. Official drugs are listed in the Revision Service, non-official drugs are not listed. The benefit of being an official drug is that the manufacturer does not have to provide documentation on provings or sufficient clinical data [14]. On the other hand, non-official homeopathic drugs must provide provings information to the FDA in order to determine its status as a homeopathic drug [14].

C. Recent Developments & Aggravating Factors

Although homeopathy started as a small market, it is currently growing exponentially and is an approximately three-billion-dollar industry [15]. Accordingly, an increasing number of patients are subject to homeopathic treatments with potentially harmful effects due to their unsubstantiated health and safety claims [15]. Furthermore, untested homeopathic treatments may divert patients from conventional medical diagnosis and treatments, which may lead to harm or even death [16]. Homeopathic drug efficacy typically amounts to a placebo effect at most when tested with the rigorous standards of conventional medicine [17]. Thus, patients’ substitution of conventional drugs, which have clinically proven effects, with homeopathic treatments is a serious concern because it may produce the perception of getting better without diminishing the cause of symptoms [17]. Considering the direct and indirect risks of homeopathic treatments—potentially harmful products and potential consequences of delaying or forgoing proven conventional medicine, respectively—a risk-based approach is the appropriate way to protect patients from unknown adverse outcomes of homeopathic treatments.

III. Risk-Based Approach Appropriately Addresses Concerns of Homeopathic Drugs

As outlined in the previous section, the need for increased regulation of drugs labeled as homeopathic is driven primarily by the direct and indirect risks posed by consumer reliance on the homeopathic label. These risks represent public health issues that, given industry growth, require the FDA's attention. As a result of industry growth, feasibility of enforcement as well as agency constraints need to be considered when addressing the public health concerns. The risk-based approach both addresses growing concerns about the safety and efficacy of homeopathic drugs and the increased usage throughout the country. As a result, the FDA's risk-based enforcement approach and priority enforcement categories are appropriate for addressing these concerns.

As part of the risk-based approach, public health concerns are addressed in the form of prioritized categories of enforcement. In order to fully understand the underlying public health concerns, it is important to consider how homeopathic drugs currently affect the public's health. As noted, consumers rely on homeopathic labels for information but those labels may not clearly indicate the difference in safety and efficacy requirements of homeopathic versus conventional drugs. The minimal publicly available data regarding homeopathic drug use suggests homeopathic drugs are chiefly used for self-treatment and are not typically physician-prescribed [18]. This means consumers decide for themselves, based on available information, whether a drug is safe and effective. Homeopathic products are sought out primarily because they are believed to be safe and effective forms of self-treatment [18]. This potential disconnect between beliefs about safety and efficacy and substantiation of those beliefs by FDA standards poses public health concerns. The lack of valid information and the self-treatment motivation both factor into the potential for consumers to attribute the safety and efficacy of conventional drugs to homeopathic products. The misunderstanding of and lack of information about homeopathic products, in combination with their potential risks, comprise public health concerns that the prioritized categories are meant to address.

The priority enforcement categories identified by the FDA draft guidance for industry are appropriate, due to greater magnitude of risk associated with homeopathic drug usage in relation to these categories. However, we have additional recommendations and considerations for FDA's application of risk-based enforcement for these categories that are included in the following section.

IV. Prioritizing Vulnerable Populations

In light of the risk-based approach, we recommend the FDA treat vulnerable populations as an overarching risk category with even higher priority than the other five risk categories. In addition, we recommend the FDA amend its definition of “vulnerable populations” to include individuals made vulnerable by SDH, as this will more fully capture the individuals who may be vulnerable to harmful unapproved drug products labeled as homeopathic.

In addition, we recommend the FDA incorporate SDH into its enforcement guidelines. SDH are defined by the World Health Organization (WHO) as the broad structural determinants and conditions of daily life that have strong influences on a person’s health outcomes [19]. SDH are often caused by the unequal distribution of power, resources, and income, among other things, both within and between countries [19]. The unequal distribution of power and resources affects all aspects of daily life, and the health of people who do not have access to power and resources is adversely affected [19].

A. Broadening the Definition of "Vulnerable Populations"

A growing body of research demonstrates the importance of SDH for reducing adverse health outcomes. The draft guidance defines vulnerable populations as strictly biologically vulnerable populations through the examples in the list of prioritized categories for regulation and enforcement. While this is an important group for the FDA to include, we suggest the FDA consider socially vulnerable populations in addition to biologically vulnerable ones because of the importance of SDH at predicting health outcomes.

A 2010 consideration on the public health issues related to complementary and alternative medicine (CAM) noted several categories of risk to consider related to public health [20]. The language is strikingly close to the language set forth in the current draft guidance for industry. Additionally, the consideration of “risk to special populations” in that discussion parallels the vulnerable populations in the current draft guidance. These populations are of particular concern to regulators because most public health risks have not been evaluated in vulnerable populations [20]. In essence, the lack of data and research puts certain groups at increased risk of harm. However, what is known about homeopathic drug use suggests it is necessary and appropriate to begin regulating their use.

B. The Need for Data

The trends in current homeopathic data suggest the average user of homeopathic drugs is a white, educated female. This is not the typical vulnerable population disadvantaged by SDH, which often focus on the absence of a resource due to power imbalances. However, rather than homeopathic drug usage directly indicating lack of access to healthcare, education, or other SDH, it could instead indicate an abundance of information or resources unavailable to another population. Thus, groups disadvantaged by SDH standards may not use homeopathic drugs as often as the majority user group

because they don't have the resources or power that would enable them to pursue these options [21]. Just because groups disadvantaged by SDH are not the most likely to suffer the harms of homeopathic drugs because they are not the most likely to use them does not mean they are not affected [21]. By using homeopathic products, already disadvantaged or vulnerable populations could in fact hurt the most on an individual level if they incur a harm because of their lack of access to resources and information.

While few studies comparing homeopathic usage to conventional medicine have been performed in the United States, several European countries have carried out focused, within-group comparison studies. A study by Italia, et al., compared conventional and alternative pharmaceutical usage in children in Germany [22]. This study used Germany's FDA parallel—the German Federal Institute for Drugs and Medical Devices (BfArM)—to compare the use of the three major categories of drugs within the BfArM structure: conventional, homeopathic, and phytotherapeutic [22]. They found conventional and phytotherapeutic usage decreased with income, while homeopathic use increased with income. They suggested this trend may be related to an “open-minded higher education status” when used moderately and in an additive or complementary form, but utilization to the exclusion of all conventional medicine may be related to lower education [22]. Given the large impact education can have on overall long-term health outcomes, this is an important trend for the FDA to consider when regulating homeopathic drugs.

However, we recognize assessing the presence of SDH may be hampered by an absence of data on the consumers of products labeled as homeopathic. When developing enforcement and regulatory action, representative data is necessary to determine who is using homeopathic drugs, what illnesses are being treated, and to assess risks and benefits. Without sufficient and accurate data, issues that specifically affect the groups included in the priority categories will not be addressed.

V. Demographics of Homeopathic Drug Consumers

We know very little about consumers of homeopathic drugs for a number of reasons. First, there is a lack of research in this area. Second, the small amount of existing research on homeopathy is often bundled with CAM research. This makes it hard to assess who uses homeopathic drugs because the research does not often break down demographics by category of drugs. Third, most homeopathy users self-prescribe and do not consult with specialized practitioners, making it more difficult to obtain consumer demographic information. However, the following discussion examines the minimal existing data, such as the prevalence of homeopathic drug use and the characteristics of homeopathic drug consumers from government and industry surveys. The available data suggest pregnant women, their children, and those who cannot access health care are particularly vulnerable to the risks of homeopathic drugs.

A. The Prevalence of Homeopathy

Available data suggest reliance on homeopathic drugs is concentrated in distinct demographic groups in the U.S. These groups represent a significant proportion of the population. According to the

National Health Interview Survey, approximately 5 million adults and 1 million children used homeopathy in 2011 [23]. In another study, a systematic review was conducted to analyze data from various U.S. government-sponsored health surveys [24]. This systematic review estimated 3.1% of adults and 1.3% of children used homeopathy in 2016 [24].

B. Results from Government-Sponsored Surveys

There are more industry-sponsored surveys of homeopathic medicine compared to government sponsored research. From an empirical standpoint, government sponsored research is generally preferred because the data is less likely to be biased and more representative of the general population than data surveys from homeopathic industries.

In 2012, a government study analyzed homeopathic data from the National Health Interview Survey (conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) [18]. In this study, there were 718 respondents who reported using homeopathic treatments [18]. On average, homeopathic users were more likely to be Caucasian, female, married, highly educated, age 30 to 44, and located in the west of the US [18].

This study also revealed most homeopathic consumers self-prescribe treatment [18]. Of the 718 respondents, 81% self-prescribe treatments and products, while only 19% reported seeing a homeopathic practitioner for treatment [18]. Furthermore, respondents who consulted with homeopathic practitioners were significantly more likely to report homeopathy was very important to maintaining their health [18]. And finally, one-third of total respondents reported using homeopathic therapies to treat head and chest colds [18].

C. Results from Industry-Sponsored Surveys

The demographics of homeopathic users from government-sponsored surveys are analogous to surveys conducted by homeopathic industries. In 2014, the American Medical College of Homeopathy conducted an extensive survey with homeopathic patients in Canada and the U.S. by enrolling homeopathic practitioners to distribute the surveys to their patients [25]. Of the 1,054 respondents, 85% of respondents were female (Figure 1), 85% were Caucasian, 67% were married, and the average age was between 41 and 60 years old (Table 1, Appendix A) [25]. Individuals using homeopathic medicine most commonly had a bachelor's degree [25]. A majority of respondents resided in the United States, specifically in California [25]. Additionally, most respondents stated they sought homeopathic treatment for general health reasons [25]. Finally, over 85% of respondents mentioned they paid for homeopathic treatment out-of-pocket, while only about 4% paid with insurance [25].

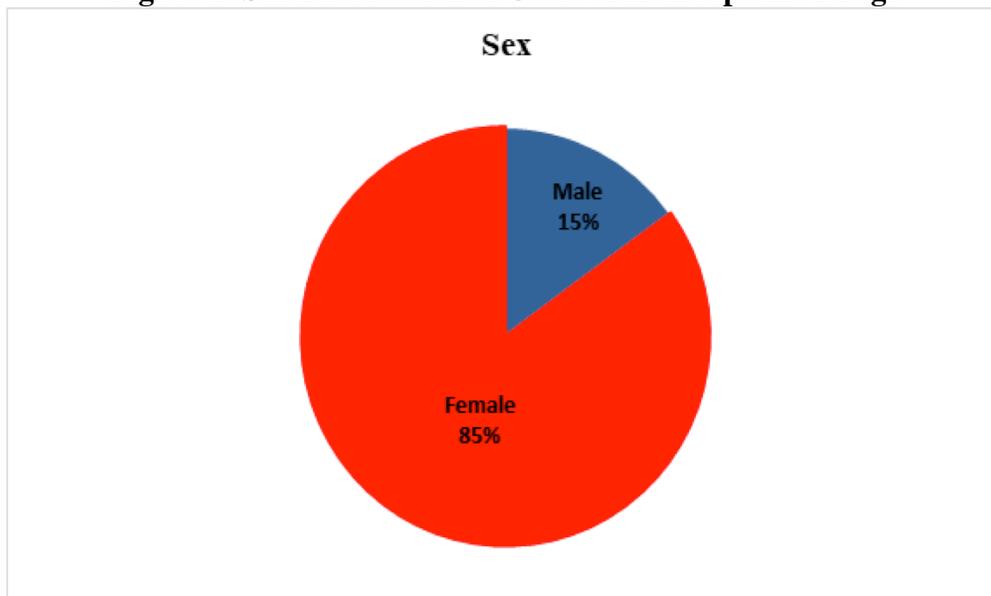
These data highlight the importance of prioritizing potentially vulnerable populations as a factor in regulation of homeopathic drugs. For example, the overwhelming proportion of homeopathic drug consumers are notably married women (Figure 1), suggesting that pregnant women could also be a potential class of consumers. Children and pregnant women are considered vulnerable populations [26]. Therefore, given the lack of research on the safety and efficacy of homeopathic drugs, it is critical for the FDA guidance to consider all potential consumers, specifically groups that may be overlooked such as pregnant women, children, and low socioeconomic status individuals. These points all support the importance of expanding the current definition of the vulnerable population category in the FDA draft guidance to include SDH.

After examining the few existing surveys from both government and industry, the average homeopathic user is a white, married female, with at least a bachelor’s degree, residing in California. These individuals primarily use homeopathic remedies for general health purposes, such as treating a cold. Therefore, it is reasonable to assume from this data that most individuals are self-prescribing therapies are for non-threatening conditions that will resolve on their own. Although, it is concerning that most users of homeopathic medicine do not seek the advice of a practitioner.

It is important to note existing data does not allow us to draw conclusions about the populations impacted by homeopathic drugs. As previously mentioned, relying on industry surveys, such as the North American Homeopathic Patient Survey, is problematic because industries have a vested interest in the results. Results may be biased due to the conflict of interest.

Additionally, because homeopathic practitioners distributed this survey, it is more likely that results are skewed due to social desirability bias. Social desirability is a type of bias where respondents self-report to conform to socially accepted values or to prevent criticism [27]. Hence, patients may feel

Figure 1: Sex Distribution of Users of Homeopathic Drugs



pressured to gain approval from their doctors and “fake good” in their responding. This form of bias can potentially invalidate the survey. Furthermore, because many individuals using homeopathic medicine do not consult with a practitioner, surveys aimed at people seeking advice from a practitioner suggests the results are not representative of all users. This group of consumers may not be a primary concern because they likely have access to health care to reduce risk of negligent harms from homeopathic drugs.

Unfortunately, due to the limited available data, we cannot assume the same for the bulk of consumers who do not consult with specialized practitioners. We do not have enough data to know where or how these individuals are getting their information on homeopathic drugs. Additionally, many of these individuals are not likely to be identified as consumers of homeopathic drugs because they cannot afford to consult with practitioners; hence, their lack of access to resources puts them at higher risk for harm. To understand the true prevalence of homeopathy, more national government-sponsored surveys should be conducted to obtain more representative samples.

VI. Summary of Recommended Approach

Finally, what follows is a brief outline of how we envision the final guidelines functioning, with our major recommendations in bold print. We hope that it may prove useful.

1. While any drug product labeled as homeopathic and marketed without FDA approval may be subject to FDA enforcement action at any time, the FDA will generally prioritize enforcement actions regarding drug products which meet the above description and which also pose significant risks to public health.
2. **Such products include, first and foremost, products for vulnerable populations (including biologically vulnerable populations, as described in the draft guidance, and socially vulnerable populations, as indicated by social determinants of health).**
3. In addition, products which pose significant risks to public health may include:
 - a. Products with reported safety concerns;
 - b. Products that contain or purport to contain ingredients associated with potentially significant safety concerns;
 - c. Products for routes of administration other than oral and topical;
 - d. Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions; and,
 - e. Products deemed adulterated under section 501 of the FD&C Act.
4. **If an unapproved drug product labeled as homeopathic is both intended for a vulnerable population and also falls into one or more of the above risk categories (items 2 and 3 above), it should be given an even higher enforcement priority than if it only fell into one risk category.**
5. **Finally, when considering any enforcement action related to unapproved drug products labeled as homeopathic, the FDA should request additional data about the users of such drugs from the manufacturers, in order to determine whether vulnerable populations are implicated.**

Thank you for considering this submission.

Respectfully submitted on March 20, 2018.

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APPENDIX A

Demographics of Homeopathic Consumers: Industry Survey

The following data in Table 1 are from the 2014 North American Homeopathic Patient Survey. These data are not inclusive to the entire survey and only selected statistics were chosen to highlight the top general demographic information on consumers.

Table 1: Demographics of Homeopathic Consumers. Data Pulled from North American Homeopathic Patient Survey. 2014. A Study Conducted by the American Medical College of Homeopathy Department of Research.

https://www.ftc.gov/system/files/documents/public_comments/2015/11/00364-99551.pdf.

Variables	Percentage (%)*
Age †	
31-40 years	13.0
41-50 years	22.0
51-60 years	30.0
61-70 years	20.0
Average age (years)	30.0
Ethnicity	
White	85.0
African American	0.9
Hispanic	3.8
Asian	5.8
Native American	0.3
Other	4.5
Sex	
Male	15.0
Female	85.0
Education Level	

High school	11.1
Associates	8.7
Bachelors	32.7
Masters	25.9
Doctoral	10.3
Location [‡]	
United States	88.0
Canada	12.0
California	12.6
Pennsylvania	6.8
Arizona	4.8
Treatment Purposes [§]	
General Health	20.6
Psychiatric	16.2
Musculoskeletal	8.1
Infectious Disease	7.7
Dermatology	5.2
Pediatrics	2.7

* Sections with parts that do not amount to a whole (100 percent) are due to inconsistent response rates.

[†] These were the top five age groups examined.

[‡] These were the top five locations examined.

[§] These were the top five reasons to seek treatment.

* Sections with parts that do not amount to a whole (100 percent) are due to inconsistent response rates.