

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

The Advisability and Feasibility of Developing USP Standards for Medical Cannabis

Gabriel I. Giancaspro, Nam-Cheol Kim, Jaap Venema, Susan de Mars, Jennifer Devine,
Carlos Celestino, Christine E. Feaster, Ben A. Firschein, Mary S. Waddell, Stephen M.
Gardner, and Earl Jones Jr.^a

ABSTRACT

This *Stimuli* article analyzes the need for public quality standards for medical cannabis (defined herein as marijuana used for medical purposes under state laws) and the potential role of the U.S. Pharmacopeial Convention (USP) in addressing that need.¹ Following legalization of the medical use of cannabis in several U.S. states and internationally, USP has received requests to investigate the advisability and feasibility of developing quality standards for medical cannabis. Development of quality standards for medical cannabis requires consideration of a wide range of scientific, legal, and policy issues that reach far beyond its classification as a botanical drug or herbal medicine. This article discusses the current regulatory and scientific landscape regarding medical cannabis, identifies issues related to the lack of quality standards for medical cannabis, and explores potential options for developing quality standards. USP seeks input from stakeholders on whether USP should proceed with development of quality standards for medical cannabis and if so, what approaches should be utilized to establish such standards.

LEGAL AND REGULATORY LANDSCAPE

The federal and state regulatory environment surrounding the medical use of cannabis involves many federal agencies and various different state laws. The evolving legal environment is an important consideration when evaluating the advisability and feasibility of USP developing a public standard for cannabis.

At this time, the U.S. Food and Drug Administration (FDA) has not approved cannabis as a safe and effective drug for any indication (1). FDA has approved one drug containing a synthetic version of a substance that is present in cannabis and another drug containing a synthetic substance that acts similarly to compounds from cannabis but is not present in cannabis. However, the FDA has not identified a medical use for cannabis.

Furthermore, the federal Controlled Substances Act classifies cannabis as a Schedule I drug, which means that its use, sale, cultivation, and distribution in the United States are illegal except for research purposes (2). As a Schedule I controlled substance, cannabis is not considered under federal law to be a drug for medical use, meaning that

it has “no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse (3).”

Although cannabis is a Schedule I controlled substance, under the Compassionate Investigational New Drug Program the federal government through the National Institute on Drug Abuse allows the University of Mississippi in Oxford, MS to cultivate, harvest, and roll cannabis into cigarettes for distribution to patients for medical needs (4). These few patients are legally permitted by the federal government (including the Drug Enforcement Administration) to smoke cannabis as a means to alleviate their medical conditions.

Despite the status of medical cannabis under federal law, 24 states and the District of Columbia have passed various forms of legislation permitting the use of medical cannabis including laws relating to the cultivation, distribution, and sale of medical cannabis (5). The U.S. Department of Justice has established a policy that it will not enforce federal laws against individuals who use cannabis for medical purposes in states that have legalized use of medical cannabis but also have robust regulatory and enforcement systems in place (6). As a result, health care providers are navigating inconsistent and conflicting laws and regulations when they prepare to prescribe, dose, and prepare formulations as well as monitor interactions between cannabis and other medications. Even in the states where use of medical cannabis is allowed, physicians are not allowed to prescribe it and can only “recommend” or “advise consideration” of cannabis therapy (7).

Outside the U.S., a number of countries have addressed the use of medical cannabis. For example, medical cannabis use has been permitted in Canada since 2001 through enactment of the *Marihuana Medical Access Regulations (Regulations)* (8). The *Regulations* permit persons who are suffering from grave and debilitating illness to use, possess, and grow cannabis for medical purposes (8). Recalls of medical cannabis in Canada have highlighted the need for quality controls and regulatory oversight (9). In 1961, the European Community classified cannabis as a Schedule IV drug and strictly controlled its use (10). However, many European countries have since decriminalized or legalized cannabis for medical use (11). In addition, several other countries, including Australia and Israel, have approved medical applications for medical cannabis.

As legalization of medical cannabis has become more prevalent, the use of medical cannabis is increasing, especially as patients and the health care community become more actively engaged in the dialogue. This increased use makes it critical to understand the scientific, quality, and public health issues surrounding medical cannabis (12).

SCIENTIFIC, QUALITY, AND PUBLIC HEALTH CONSIDERATIONS

The plant material known by the common names marijuana or marihuana consists of the dried flowers and leaves from two species of the genus *Cannabis*: *Cannabis sativa* L. and *C. indica* L.; for this reason it is also referred to as “cannabis” in many regulatory documents. As the use of medical cannabis increases, the science of cannabis composition and its related health effects is also advancing at a very fast pace. The available analytical methodology is now sufficiently evolved to allow the development of meaningful quality standards.

Biologically Active Cannabis Compounds

Several hundred secondary metabolites have been identified as constituents of cannabis. These constituents fall into diverse phytochemical classes, and the most studied class is the cannabinoids. The plant also contains other terpenoids, non-cannabinoid phenols, nitrogen compounds, and other phytoconstituents. Cannabinoids are present in the plant material, mostly in the form of inactive carboxylic acids, and are converted by heat (while smoking or baking), light, or natural degradation to their active decarboxylated counterparts. The two main active decarboxylated cannabinoids of interest are tetrahydrocannabinol (THC) and cannabidiol (CBD). Studies have shown that THC can increase appetite and reduce nausea, and the FDA has granted approval for THC-based medications for these purposes. THC may also reduce inflammation, pain, and problems with muscle control (13). CBD, a non-psychoactive cannabinoid, may be useful for reducing pain, inflammation, and epileptic seizures, and it may even help to treat mental illness and addictions (13). Recent animal studies suggest that cannabis extracts may have benefits in cancer treatments, but this animal research must be viewed as preliminary. In mice, purified THC and CBD from cannabis extract, when combined with radiation, improved the efficacy of glioma treatment (14). Scientists are also conducting preclinical and clinical trials with cannabis and its extracts to treat numerous diseases and conditions including autoimmune diseases (HIV/AIDS, multiple sclerosis, Alzheimer's disease), inflammation, pain, seizures, substance use disorders, and mental disorders. Despite this ongoing research, the FDA has yet to determine that there is sufficient data to demonstrate the safety and efficacy of medical cannabis.

Commercially Available Cannabis Compounds Used as Drugs

Clinical studies of cannabinoids isolated from cannabis as well as synthetic derivatives have led to two FDA-approved medications that contain cannabinoids in pharmaceutical dosage forms in the United States. One of these drugs is known under the generic name dronabinol (15) and marketed under the brand name Marinol. The other is a synthetic cannabinoid with the generic name nabilone, sold under the brand name Cesamet. Cesamet is approved for "treating nausea and vomiting caused by chemotherapy for cancer patients" and Marinol is for "increasing appetite and weight gain in patients with AIDS." (16) These are some of the same symptoms for which physicians recommend cannabis therapy. The United Kingdom, Canada, and 17 European countries have approved an extract of cannabis containing a mixture of natural cannabinoids, mainly THC and CBD, with the generic name nabiximols (13,17). Nabiximols is commercially available as a mouth spray with the brand name Sativex to treat muscle control problems caused by multiple sclerosis.

Clinical Studies

A search on the website ClinicalTrials.gov, maintained by the National Library of Medicine at the National Institutes of Health, revealed 202 open clinical trials for the term "cannabis" as of August 28, 2015 (18). Many of the target outcomes for these studies relate to cannabis abuse (79 studies), but many other studies are intended to research new treatments for a variety of medical conditions such as schizophrenia, cancer, autoimmune diseases, epilepsy, musculoskeletal diseases, and others. For example, a U.S. company is conducting clinical trials with nabiximols to investigate its safety in treating cancer pain (19). The need for quality specifications for the cannabis

used in these studies is self-evident, as researchers need to qualify the clinical trial material in terms of identity, purity, strength, and absence of contaminants.

Quality of Cannabis

Some states have recognized the *American Herbal Pharmacopeia* monograph in their regulations, but there are no federally recognized quality standards for medical cannabis (20). In addition, little or no quality control (QC) testing of medical cannabis is being done at the present time. As with other medications, the development of pharmacopeial quality standards for cannabis can help ensure the identity, purity, and strength of the cannabis, reduce the possibility of adulteration, and help to prevent contamination with heavy metals, solvents, or pathogenic microorganisms. Such pharmacopeial standards would provide an essential foundation to assess the quality of the material for use in subsequent clinical trials intended to demonstrate safety and efficacy of cannabis.

Concerns about safety and efficacy highlight the need for public standards that can help ensure the consistency and quality of cannabis used for medical purposes (21,22). One major concern is the wide variation in cannabinoid content among the many different varieties of cannabis (23). The cannabinoid content and composition are generally dependent on the geographical location where it is cultivated and the agricultural practices used, which take into account soil, climate, and growing processes (e.g., traditional farming, organically grown, greenhouse, hydroponic farming, and others). Production methods have been developed and strains have been bred to increase total THC content. Conversely, cultivation of cannabis can also be manipulated to produce strains with lower THC content, which can affect dosage and perpetrate fraud involving cannabis for medical purposes.

For these reasons, the chemical profile and cannabinoid content of medical cannabis can vary from species to species and plant to plant. In the Netherlands, the Ministry of Health, Welfare, and Sport has developed a set of guidelines for the indoor growing of cannabis specifically for purposes of medicinal use (24). In the U.S., the state of Colorado has developed regulations for medical cannabis that would establish strain and potency labeling requirements and pesticide limits, along with submission of random cannabis samples for state testing (25,26).

Another concern is microbial contamination, which has been identified as a serious risk because powdered cannabis can become contaminated with fecal pathogens, molds (especially *Aspergillus fumigatus*), and aflatoxins during cultivation, harvesting, drying, storage, and/or distribution (27). The need for effective use of pesticides to prevent contamination with pathogens and molds has been emphasized (28). Specifications that reduce patients' exposure to risks posed by contamination of medical cannabis could be established to help reduce these risks.

Cannabis also has a long history of adulteration, primarily to enhance its psychotropic effect. For example, in India, cannabis has been adulterated with the plants *Datura metel*, *Hyoscyamus niger*, or *Areca catechu*, possibly for cholinergic modulation (29). Hashish, a cannabis preparation made from purified stalked resin glands, has been adulterated with tobacco to help it burn properly for better drug absorption (30).

Cannabis is sometimes adulterated with other psychoactive compounds to mask the effect of cannabis with low cannabinoid content or to decrease its adverse effects (30). Other, more dangerous forms of adulteration occur when cannabis is mixed with

synthetic analogs that have activity on the cannabinoid receptors. Starting around 2004, herbal mixtures known as “K2” or “Spice” have been sold as legal alternatives to cannabis (31). These mixtures, promoted for aromatherapy, are laced with synthetic cannabinoids, chemically derived from aminoalkylindoles or from a nucleus of naphtho-keto-indole typically named with the initials JWH followed by a number (32). USP has recently addressed this issue with the development of a new general chapter, [Adulteration of Dietary Supplements with Drugs and Drug Analogs \(2251\)](#). Similar approaches could be used in developing cannabis standards to detect this type of adulteration.

Formulation processes may pose additional public health risks. As a medicine, cannabis may be presented in a variety of forms. The traditional presentation is smoking the raw plant material, and there are also several methods of concentrating active ingredients, including dry sifting kief or further processing to hash. There are also various methods of cannabis oil extraction for use as a direct oral or topical application, or for inclusion in edibles. It is important to note that many of the common methods of oil extraction use toxic organic solvents that pose a risk of chemical contamination (33). USP has developed procedures and general approaches, described in the general chapter [Residual Solvents \(467\)](#), that could be applied to cannabis formulations to help address this risk.

Pharmacopeial identification tests also could be developed to establish the identity of medical cannabis. The various USP compendia—*USP–NF*, the *Herbal Medicines Compendium*, and others—already contain relevant scientific identification procedures for other botanical articles developed in partnership with industry, other pharmacopeias, and regulatory agencies. For example, approaches described in the guideline “Monographs in the Herbal Medicines Compendium” could be followed to generate specific fingerprint profiles that would correctly identify not only the species but also the chemotype or variety of cannabis. The USP compendia contain other procedures that can aid in the identification of botanicals, such as those described in [Identification of Articles of Botanical Origin \(563\)](#) and in the recently developed new general chapters [High-Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin \(203\)](#) and [Identification of Articles of Botanical Origin by High-Performance Thin-Layer Chromatography Procedure \(1064\)](#).

HISTORY OF MEDICAL CANNABIS IN USP AND OTHER COMPENDIA

In 1850, USP admitted cannabis as a recognized drug in the *United States Pharmacopeia (USP)* and published an *Extractum Cannabis* (or *Extract of Hemp*) monograph (34). Thereafter, USP published a *Cannabis americana* monograph in 1916 (35). In 1936, USP published in *USP XI* a monograph for *Cannabis sativa* L. and also provided monographs for alcohol extracts (*Extractum Cannabis* and *Fluidextracta Cannabis*) (36). The *National Formulary (NF)* and *United States Dispensatory* also included monographs on cannabis and cited recommendations for its use for numerous illnesses (37). There has not been a marijuana or cannabis monograph published in the *USP* since its omission in 1942 (*USP XII*) (38) in response to a concerted effort by the Federal Bureau of Narcotics in the 1930s and further classification of cannabis and tetrahydrocannabinoids as Schedule I drugs in 1970.

Cannabis monographs appeared in the *British Pharmacopoeia* as early as 1888 but were removed in 1932 (39). A monograph for *Cannabis sativa* is included in the

Ayurvedic Pharmacopoeia of India, *Siddha Pharmacopoeia of India* (40), *Unani Pharmacopoeia of India*, and *Pharmacopoeia of the People's Republic of China* (41). The *American Herbal Pharmacopeia* has recently proposed a monograph for the flowers (42).

At the time of publication, the current edition of *USP–NF* contains a monograph for dronabinol, and USP is actively seeking a sponsor to develop a nabilone monograph. USP also currently offers the Reference Standards *Exo-tetrahydrocannabinol* and *Delta-9(Δ^9)-tetrahydrocannabinol* for dronabinol (43).

APPROACHES FOR DEVELOPING COMPENDIAL STANDARDS FOR CANNABIS

USP has a long history of developing quality standards for herbal medicines, either as pharmaceuticals or as dietary supplements. USP has state-of-the-art laboratories throughout the world, and global scientific expertise in the form of USP staff and expert volunteers. This cumulative experience and expertise at USP could be used as a foundation for standard development for cannabis products.

As USP considers whether and how to pursue the development of quality standards for cannabis, ongoing public input and stakeholder participation will be critical. In addition to soliciting input through this *Stimuli* article, USP is considering organizing an open forum for discussion of these proposals to gather input for a suitable path forward toward the potential development of quality standards for medical cannabis.

If development proceeds, USP has a number of different options to ensure that appropriate scientific expertise is engaged in the standards-setting process. These include forming an Expert Panel under USP's Botanical Dietary Supplements and Herbal Medicines Expert Committee to bring in additional technical expertise and broaden representation of affected stakeholders. This Expert Panel would make recommendations on standards to the Expert Committee, which is the decision-making body for USP standards in this area. USP could issue a public call for candidates to help ensure that all interested experts have the opportunity to participate in the development of cannabis standards.

Another important consideration would be where to publish the standards that USP may develop for medical cannabis. USP's flagship compendia, the *USP–NF*, are recognized as "official compendia" under United States law and contain standards for identity, strength, quality, and purity of medicines that are enforceable by the FDA. Generally, *USP–NF* only contains monographs for drugs that were included in *USP* before the 1938 amendment to the Food, Drug and Cosmetic Act, or drugs that are legally marketed in the U.S., which presents an important challenge given that marijuana is currently illegal under federal law. Given medical cannabis' current legal status, the regulatory implications of publishing cannabis standards in *USP–NF* would need to be carefully reviewed and analyzed with input from regulators and other stakeholders. In particular, input from the FDA and U.S. Drug Enforcement Administration will be critical.

Another option for publication would be USP's *Herbal Medicines Compendium (HMC)*, an online compendium dedicated to traditional/herbal medicines and launched in 2013. The scope of herbal articles eligible for inclusion in the *HMC* is limited to articles that 1) are approved by a national authority for use as ingredients of herbal medicines, or are included in a national pharmacopeia; and 2) are deemed appropriate for inclusion in the *HMC* by a USP Expert Committee (44). Standards in the *HMC* are developed through

the same process as *USP–NF* standards, including a public review and comment period and approval by the Botanical Dietary Supplements and Herbal Medicines Expert Committee. A third option would be to develop stand-alone USP guidelines for the quality of medical cannabis, not included in any particular compendium. If medical use of cannabis were federally recognized in the future, a version of the guideline appropriately adapted in monograph format could be proposed as a *USP–NF* standard through the typical *USP–NF* revision process.

As the use of medical cannabis is growing, the need for a USP public scientific standard to help ensure identity, purity, quality, and strength has been identified. Public quality standards for medical cannabis are important for many reasons, including the avoidance of adulteration, accurate identification, control of contaminants, and considerations regarding constituent composition and strength.

CONCLUSION

USP is committed to working with stakeholders to determine the advisability and feasibility of developing public quality standards for medical cannabis. USP welcomes comments on the issues and ideas presented in this *Stimuli* article and on all aspects of developing such standards, including scientific and public health considerations, legal and regulatory issues, and mechanisms for obtaining appropriate scientific expertise and ongoing stakeholder input.

REFERENCES

1. Food and Drug Administration. FDA and marijuana. Silver Spring, MD: FDA; 3 March 2013.
<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm>
2. United States Department of Justice. Drug Enforcement Administration. Office of Diversion Control. Title 21 United States Code (USC) Controlled Substances Act. Subchapter I – Control and enforcement. Part B – Authority to control; standards of controlled substances. §812. Schedules of controlled substances. (b) Placement on schedules; findings required. (1) Schedule I. Springfield, VA: U.S. Department of Justice; 1970. [also known as Controlled Substances Act, 21 United States Code § 812(b)(1), 1970]
<http://www.deadiversion.usdoj.gov/21cfr/21usc/812.htm>
3. United States Department of Justice. Drug Enforcement Administration. Office of Diversion Control. 21 CFR Chapter II. Denial of petition to initiate proceedings to reschedule marijuana. Springfield, VA: U.S. Department of Justice; 8-Jul-2011. http://www.deadiversion.usdoj.gov/fed_regs/rules/2011/fr0708.htm
4. ProCon.org. What is the US government's compassionate investigational new drug (IND) program for medical marijuana? Santa Monica, CA: ProCon.org; 2015.
<http://medicalmarijuana.procon.org/view.answers.php?questionID=000256>
5. National Conference of State Legislatures. State medical marijuana laws. [Medical marijuana is currently allowed in 24 states, including: Alaska, Arizona, California, Colorado, Connecticut, Delaware, Guam (a U.S. territory), Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode

- Island, Vermont, and Washington, and the District of Columbia.] Washington, DC: National Conference of State Legislatures; 2015.
6. United States Department of Justice. Office of the Deputy Attorney General. Guidance regarding marijuana enforcement. Springfield, VA: U.S. Department of Justice; 29 Aug 2013.
<http://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf>
 7. Marcoux RM, Larrat EP, Vogenberg FR. Medical marijuana and related legal aspects. *P&T*. 2013;38(10):612, 615–619.
 8. Government of Canada. The Minister and Attorney General. Marijuana medical access regulations (Sor/2001-227) [modified 02 Sep 2015]. Ottawa, Canada: Health Canada; 2001. <http://laws-lois.justice.gc.ca/eng/regulations/SOR-2001-227/index.html>
 9. Government of Canada. Healthy Canadians. Recall of marijuana for medical purposes – Tilray [RA-52663]. Ottawa, Canada: Health Canada; 20 Mar 2015. <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/52663a-eng.php>
 10. United Nations. Single convention on narcotic drugs, 1961 [as amended by the 1972 protocol]. https://www.unodc.org/pdf/convention_1961_en.pdf
 11. Frazzetto G. Does marijuana have a future in pharmacopoeia? *EMBO Rep*. 2003;4(7):651–653.
<http://onlinelibrary.wiley.com/doi/10.1038/sj.embor.embor893/pdf>
 12. Evans DG. The economic impacts of marijuana legalization. *J Global Drug Policy Pract*. 2013; 7(4):1–39. <http://jpo.wrlc.org/handle/11204/3240>
 13. National Institute on Drug Abuse. DrugFacts: Is marijuana medicine? Bethesda, MD: NIDA; July 2015:1–4.
<http://www.drugabuse.gov/publications/drugfacts/marijuana-medicine>
 14. Scott KA, Dalgleish AG, Liu WM. The combination of cannabidiol and Δ^9 -tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model. *Mol Cancer Ther*. 2014;13(12):2955–2967.
<http://www.ncbi.nlm.nih.gov/pubmed/25398831>
 15. United States Pharmacopeia. *USP 38–NF 33* [official May 1, 2015]. Baltimore, MD: United Book Press; 2014.
 16. National Institutes of Health. U.S. National Library of Medicine. MedlinePlus. Dronabinol. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a607054.html>. Nabilone. <https://www.nlm.nih.gov/medlineplus/druginfo/meds/a607048.html>
 17. Bifulco M, Pisanti S. Medical use of cannabis in Europe. *EMBO Rep*. 2015;16(2):130–132.
<http://onlinelibrary.wiley.com/doi/10.15252/embr.201439742/abstract>
 18. United States National Institutes of Health. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/results?term=cannabis&recr=Open>
 19. United States National Institutes of Health. ClinicalTrials.gov. Long term safety of Sativex® oromucosal spray (Sativex®; Nabiximols) as adjunctive therapy in patients with uncontrolled persistent chronic cancer related pain. <https://clinicaltrials.gov/ct2/show/NCT01337089>
 20. Despres H. Cannabis testing: a review of the current landscape. *Am Oil Chem Soc*. 2014; AOCC Press, Inform: May.

21. Halford B. Chemists analyze cannabis for safety and potency. *Chem Eng News*. 2013;91(49):32–33. <http://cen.acs.org/articles/91/i49/Chemists-Analyze-Cannabis-Safety-Potency.html>
22. Kemsley J. Making legal marijuana safe. *Chem Eng News*. 2015;93(16): 27–28. <http://cen.acs.org/articles/93/i16/Making-Legal-Marijuana-Safe.html>
23. Office of National Drug Control Policy. Marijuana: know the facts. October 2010. <https://www.whitehouse.gov/ondcp/ondcp-fact-sheets/marijuana-know-the-facts>
24. Office of Medicinal Cannabis. [explanation of government agency.] Den Haag, The Netherlands. <https://www.cannabisbureau.nl/english>
25. The Washington Post [newspaper]. Colorado grapples with effort to create the first state marijuana regulations. Washington, DC: The Washington Post, November 27, 2010. <http://www.washingtonpost.com/wp-dyn/content/article/2010/11/26/AR2010112604714.html>
26. State of Colorado. Department of Revenue. Marijuana Enforcement Division. Permanent rules related to the Colorado medical marijuana code. September 9, 2013. https://www.colorado.gov/pacific/sites/default/files/Medical%20Marijuana%20Rules%20-%20ADOPTED%20090913,%20Effective%2010152013_0.pdf
27. Cundell T. Microbiological attributes of powdered cannabis. *Am Pharm Bus Tech*. July 31, 2015. <http://www.americanpharmaceuticalreview.com/Featured-Articles/177487-Microbiological-Attributes-of-Powdered-Cannabis/>
28. Borl B. The wild west of marijuana pesticides. *The Atlantic*. August 31, 2015. <http://www.theatlantic.com/health/archive/2015/08/pot-marijuana-pesticide-legalization/401771/>
29. McPartland JM. Adulteration of cannabis with tobacco, calamus, and other cholinergic compounds. *Cannabinoids*. 2008; 3(4):16–20.
30. McPartland JM, Blanchon DJ, Musty RE. Cannabimimetic effects modulated by cholinergic compounds. *Addict Biol*. 2008;13:411–415. <http://www.ncbi.nlm.nih.gov/pubmed/18782385>
31. National Institute on Drug Abuse. DrugFacts: K2/spice (“synthetic marijuana”). Bethesda, MD: NIDA; 2012: 1–2. <http://www.drugabuse.gov/publications/drugfacts/k2spice-synthetic-marijuana>
32. Spice/K2 drugs—more than innocent substitutes for marijuana. *Int J Neuropsychopharmacol*. 2014;17(3):509–525. <http://www.ncbi.nlm.nih.gov/pubmed/24169044>
33. Rosenthal E, Downs D. Beyond buds: marijuana extracts—hash, vaping, dabbing, edibles and medicines. [ebook]: Quick American Archives; 2014.
34. United States Pharmacopoeial Convention. *United States pharmacopoeia*, 3rd ed. Philadelphia, PA: Lippincott, Grambo & Co.; 1851.
35. United States Pharmacopoeial Convention. *United States pharmacopoeia*, 9th ed. Philadelphia, PA: P. Blakiston’s Son & Co.; 1916.
36. United States Pharmacopoeial Convention. *United States pharmacopoeia*, 11th ed. Easton, PA: Mack Printing Company; 1936.
37. History of medical cannabis. [websearch summary] [“In 1854, the United States Dispensatory listed many uses of cannabis extracts, recommending cannabis preparations for cases of neuralgia, gout, tetanus, hydrophobia, cholera,

convulsions, spasticity, hysteria, depression, insanity, and uterine hemorrhage, and also for promoting relaxed contractions during delivery.”]

<http://cannabismedicdictionary.com/history-of-medical-cannabis/>

38. United States Pharmacopeial Convention. *United States Pharmacopoeia*, 12th ed. Easton, PA: Mack Printing Company; 1942.
39. Cannabis: the scientific and medical evidence. In: House of Lords report, November 4, 1998.
<http://www.ukcia.org/research/CannabisTheScientificAndMedicalEvidence.php>
40. Government of India, Ministry of Health and Family Welfare. *The Ayurvedic pharmacopoeia of India*. Part 1, vol. 1. Vijaya. 2001:166–167.
41. *The pharmacopoeia of the Peoples Republic of China*. Vol. 1. Cannabis fructus. Beijing, China: China Medical Press; 2010:87.
42. *American herbal pharmacopoeia*. Cannabis inflorescence. New York: CRC Press, Taylor & Francis; 2013.
43. United States Pharmacopeial Convention. USP Catalog. Baltimore, MD: United Book Press, Inc.; 2015:173, September–October.
44. United States Pharmacopeial Convention. *Herbal medicines compendium*, General notices. USP [online only]: 20 May 2013.
http://hmc.usp.org/sites/default/files/documents/HMC/GN_Resource/2014-09-30%20HMC%20GN%20Update.pdf

^a Correspondence should be addressed to: Gabriel I. Giancaspro, Vice President, Science-DS & Herbal Medicines, US Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. +1.301.816.8343; e-mail: gig@usp.org.

¹ For purposes of this *Stimuli* article the terms “marijuana” and “cannabis” are synonymous and used interchangeably. The term “medical cannabis” is used for convenience to refer to marijuana used for medical purposes under various state laws, recognizing that under federal law there currently is no accepted medical use for marijuana.