Cannabis for Medical Use: FDA and DEA Regulation in the Hall of Mirrors

Rebecca S. Eisenberg[1] & Deborah B. Leiderman[2]

Casual observers could be forgiven for believing – incorrectly – that the medical use of cannabis is lawful today in the 31 states (plus the District of Columbia, Guam, and Puerto Rico) that have passed laws purporting to authorize such use.[3] But notwithstanding these state laws, cannabis remains controlled under interrelated international and U.S. federal regulatory regimes that the states may not set aside.[4] Although the legal texts that govern these regimes leave room for some medical and scientific use of controlled substances as permitted by national laws, the use of cannabis for medical treatment still violates U.S. law. The U.S. Food and Drug Administration (FDA) has approved the use of synthetic and purified products that are similar to constituents found in cannabis as safe and effective for some medical indications, but it has not yet approved the use of cannabis[5] itself for any indication. Meanwhile, the U.S. Drug Enforcement Administration (DEA) continues to classify cannabis as a Schedule I controlled substance under the Controlled Substances Act of 1970 (CSA) based in part on repeated findings – supported by analysis and recommendations from FDA – that it has "no currently accepted use in treatment in the United States."[6]

---

[1] Robert & Barbara Luciano Professor of Law, University of Michigan Law School
[2] CNS Drug Consulting LLC. MD, MA, FAAN, previously served as Director, Controlled Substance Staff, at FDA, and as Clinical Trials program director at NIDA/ NIH.
[3] The National Conference of State Legislatures maintains compendium of these laws at http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.
[4] For a history of these regimes see John J. Cohrrsen & Lawrence H. Hoover, *The International Control of Dangerous Drugs*, 9 J. Int'l L. & Econ. 81 (1974).
[5] We use the term "cannabis" rather than the term "marihuana" used in the Controlled Substances Act, Pub. L. 91-513, 84 Stat. 1242 (Oct. 27, 1970), codified as amended at 21 U.S.C. §§ 801 et seq. (CSA). The CSA defines "marihuana" as follows:

> The term "marihuana" means all parts of the plant Cannabis staiva L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalkls, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

21 U.S.C. § 802(16).
[6] 21 U.S.C. § 712(b)(1)(B).

It is a criminal offense to manufacture or distribute any Schedule I controlled substance without a license from the DEA.[7] Since 1968, the National Center for Natural Products Research at the University of Mississippi (NCNPR) has been the only registered manufacturer of cannabis for research purposes, operating under a government contract administered by the National Institute on Drug Abuse (NIDA) within the National Institutes of Health (NIH).[8] This means that clinical trials of cannabis in patients may not use the products that are currently distributed in states with medical marijuana laws, but must instead use the NCNPR-NIDA product. Such trials would also require an FDA-regulated investigational new drug application (IND). Although some researchers have conducted small studies of cannabis under INDs, none has yet obtained FDA approval of a new drug application (NDA) for cannabis, and repeated petitions to DEA to reschedule cannabis have so far failed.

Nonetheless, doctors are prescribing and patients are using cannabis for medical purposes in the U.S.[9] Although some of this purported medical use may be recreational use in camouflage, some of it represents good faith efforts on the part of treating physicians to provide health care for patients. In a 2013 online poll hosted by the New England Journal of Medicine, 76% of participating doctors in North America responded that they would recommend the use of medicinal marijuana for a hypothetical patient undergoing chemotherapy for metastatic breast cancer.[10] But the attitidues and practices of treating physicians are not the measure of "currently accepted medical use in treatment in the United States" as that language has been interpreted by the courts and agencies that administer U.S. drug laws.

Although these state-authorized uses remain illegal under federal law, without the enforcement muscle of state and local governments to back them up, the federal government does little to stop them. The legal and political environment for medical cannabis has changed considerably since Congress passed the CSA in 1970. The fact that 31 states and the District of Columbia have sought to make medical use of cannabis lawful within their borders – generally through voter referenda – is powerful evidence of considerable popular support within the U.S.

The international legal regime that led the U.S. to pass the CSA shows similar signs softening towards medical use of cannabis. The CSA brought US law into compliance with international treaties that require member states to control

---

[7] 21 U.S.C. § 822(a)(1).
[8] U.S. Dep't. of Justice, Drug Enforcement Admin., Lyle E. Craker – Denial of Application, 74 Fed. Reg. 2101-2133 (Jan. 14, 2009)(hereinafter Craker Denial).
[9] Wilson M. Compton et al., Use of Marijuana for Medical Purposes in the United States, 317 J. Am. Med. Ass'n. 209 (2017).
[10] Jonathan E. Adler & James E. Colbert, Medicinal Use of Marijuana – Polling Results, N. Eng. J. Med. Online, https://www.nejm.org/doi/full/10.1056/NEJMclde1305159 (May 30, 2013); case vignette available at https://www.nejm.org/doi/10.1056/NEJMclde1300970.

cannabis, and DEA cites these treaties in support of its regulatory moves. But some 30 other countries, including many member states, now permit medical use of cannabis under their national laws.[11] Recently the World Health Organization (WHO) sought input from Ministers of Health of member states in preparation for a special session of an Expert Committee on Drug Dependence "to review cannabis and cannabis-related substances on their potential to cause dependence, abuse and harm to health, and potential therapeutic applications" so that WHO can "make recommendations to the UN Secretary-General on the need for and level of international control of these substances."[12]

The role of FDA in timing the availability of new medical technologies has also evolved in the decades since longstanding interpretations of CSA standards for "currently accepted medical use" were put in place. U.S. federal statutory standards for showing safety and efficacy for new drugs have not changed explicitly.[13] But newer statutory provisions have encouraged FDA to shift towards earlier initial approval of many new products on the basis of less definitive premarket evidence, while monitoring future data from ongoing studies for further evidence of safety and effectiveness after the product has entered clinical use. Most medical devices and dietary supplements may be marketed with even less premarket evidence. Earlier approval of more products prior to completion of the kinds of studies that

---

[11] Sean Williams, These 30 Countries Have Legalized Medical Marijuana in Some Capacity, The Motley Fool (July 21, 2018), https://www.fool.com/investing/2018/07/21/these-30-countries-have-legalized-medical-marijuan.aspx.

[12] Dept of Health & Human Serv., Food & Drug Admin., International Drug Scheduling; Convention on Psychoropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahycrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; Requests for Comments, 83 Fed. Reg. 15155, 15156 (April 9, 2018)

[13] These standards require submission to FDA of "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" as part of a new drug application, 21 U.S.C. § 355(b)(1)(A), and direct FDA to refuse approval if the investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" or if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," with "substantial evidence" defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d).

previously would have been necessary in the premarket stage to satisfy FDCA standards for "adequate and well-controlled studies proving efficacy" for new drugs blurs the boundary between research and clinical use, calling into question the meaning of "currently accepted medical use" under the CSA.

Finally, following a string of victories for the "right to try" movement in state legislatures, the federal Right to Try Act of 2017 was recently signed into law.[14] The new legislation authorizes sponsors of new drugs to provide some patients with access outside clinical trials to investigational drugs that remain in development following completion of Phase I trials. Although FDA previously authorized more limited access to products in development under the heading of "compassionate use,"[15] the new legislation sends a clear signal to FDA that Congress favors expanding patient access to investigational drugs for which studies to date do not yet satisfy FDA approval standards.

Although none of these developments alone provides a clear basis for challenging the decisions of DEA and FDA on the legal status of medical cannabis, considered together they may give these agencies reason to reassess their interpretations of their statutory mandates in order to encourage more research into the effects of cannabis in patients. Strict scientific standards that FDA has used successfully to motivate the pharmaceutical industry to conduct rigorous trials of proprietary new chemical entities may set impossible barriers to the study of a product like cannabis. Impossible barriers may be tolerable to law enforcement authorities whose primary concern is avoiding the harms caused by the illegal drug trade. But they do little to encourage the provision of better data on the effects of cannabis in patients. The paradoxical result of such strict standards could be to discourage the cannabis industry from investing in clinical trials, leaving doctors and patients with less information to guide their use of medical cannabis rather than more. In other contexts where strict premarket approval standards would impose unsustainable research burdens on continued provision of products such as medical devices and dietary supplements, FDA and Congress have sometimes adapted the regulatory regime to make it more workable and less burdensome.[16] Following these examples, rather than attempting to meet current regulatory

---

[14] Pub. L. No. 115-176, 132 Stat. 1372 (2018).

[15] 21 CFR part 312, subpart I; U.S. Food & Drug Admin., Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers, Guidance for Industry (as updated 2017), https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf.

[16] Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified as amended at 21 U.S. Code § 360c et seq.); Dietary Supplement Health & Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325(1994) (codified as amended in scattered provisions of 21 U.S.C.).

requirements, the cannabis industry may find it quicker and easier to seek relief from Congress.[17]

We begin with a brief review in Section I of key features of the governing legal texts, including the Single Convention on Narcotic Drugs (Single Convention),[18] the CSA, and the FDCA. Section II examines more closely the relationship between scheduling decisions under the CSA and new drug approval standards under the FDCA, focusing on judicial and regulatory analysis in the context of petitions to reschedule cannabis. Section III considers special obstacles to obtaining FDA approval for cannabis, including burdens imposed on the use of Schedule I controlled substances in research, challenges in obtaining approval of botanical products, and challenges in overcoming substantial evidence of abuse potential and side effects generated over decades of government-funded research. Section IV reviews changes in the time course for FDA approval in the years since passage of the CSA to permit earlier access to various kinds of medical technologies while further safety and efficacy studies continue, and asks whether the meaning of the phrase "currently accepted medical use" should be reconsidered in light of these changes. Section V concludes.

---

[17] Numerous bills have been introduced, including one that President Trump has indicated he would probably sign into law: The Strengthening the Tenth Amendment Through Entrusting States (STATES) Act, S.3032, co-sponsored by Republican Cory Gardner of Colorado and Democrat Elizabeth Warren of Massachusetts. See John Wagner & Colby Itkowitz, Trump says he would 'probably' sign bill to protect states that have legalized marijuana,, Washington Post (June 8, 2018), https://www.washingtonpost.com/politics/trump-say-he-probably-will-support-bill-to-protect-states-that-have-legalized-marijuana/2018/06/08/23fe0884-6b24-11e8-bea7-c8eb28bc52b1_story.html?utm_term=.2d27a86fc386.

[18] Single Convention on Narcotic Drugs, *opened for signature* March 30, 1961, 18 U.S.T. 1407, 30 T.I.A.S. No. 6298, 520 U.N.T.S. 151, as amended ("Single Convention").