

University of Michigan Law School

University of Michigan Law School Scholarship Repository

Articles

Faculty Scholarship

2019

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

Rebecca S. Eisenberg
University of Michigan Law School
Deborah B. Leiderman

Available at: <https://repository.law.umich.edu/articles/2315>

Follow this and additional works at: <https://repository.law.umich.edu/articles>



Part of the [Food and Drug Law Commons](#), and the [Health Law and Policy Commons](#)

Recommended Citation

Eisenberg, Rebecca S. and Deborah B. Leiderman. "Cannabis for Medical Use: FDA and DEA Regulation in the Hall of Mirrors." *Food and Drug Law Journal* 74 (2019): 246-279.

This Article is brought to you for free and open access by the Faculty Scholarship at University of Michigan Law School Scholarship Repository. It has been accepted for inclusion in Articles by an authorized administrator of University of Michigan Law School Scholarship Repository. For more information, please contact mlaw.repository@umich.edu.

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

REBECCA S. EISENBERG AND DEBORAH B. LEIDERMAN*

ABSTRACT

A majority of Americans now live in states that purport to authorize medical use of cannabis, although federal law continues to prohibit both recreational and medical use. The current legal regime for cannabis is unstable and may be more effective at deterring research than it is at deterring medical use. Lack of data on medical cannabis products poses public health risks as well as policy and legal challenges. Modified regulatory approaches for other kinds of products provide alternative models for encouraging safety and effectiveness research and providing better information about cannabis products already in clinical use.

INTRODUCTION

Thirty-four states (plus the District of Columbia, Guam, and Puerto Rico) have passed laws purporting to authorize the medical use of cannabis.¹ Yet use of cannabis for any purpose remains controlled under U.S. federal law and international treaties that states may not override.² International agreements leave room for national laws to permit medical and scientific use of controlled substances, and some 30 nations have laws authorizing the medical use of cannabis.³ But U.S. law continues to prohibit not only the medical use of cannabis but even research using cannabis from the private growers—none registered with the Drug Enforcement Administration—who supply the medical cannabis market.⁴ In recent years, the U.S. Department of Justice has

* Rebecca S. Eisenberg is the Robert & Barbara Luciano Professor of Law, University of Michigan Law School.

Deborah B. Leiderman, MD, MA, FAAN, is Principal Drug Development and Regulatory Consultant at CNS Drug Consulting LLC. and previously served as Director, Controlled Substance Staff at FDA, and as Clinical Trials program director at NIDA/ NIH.

We gratefully acknowledge helpful comments and suggestions on earlier drafts of this paper from Howard Bromberg, Hank Greely, Erika Lietzan, Sean O'Connor, Kyle Sampson, and participants in the "FDA Past, Present, & Future" conference at American University Washington College of Law, October, 2018.

¹ NAT'L CONF. OF STATE LEGISLATURES, *State Medical Marijuana Laws* (2019), <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> [<https://perma.cc/C8RE-T826>].

² See generally John J. Cochrane & Lawrence H. Hoover, *The International Control of Dangerous Drugs*, 9 J. INT'L L. & ECON. 81 (1974).

³ 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> [<https://perma.cc/EM5D-3AXT>] [hereinafter *Williams Motley Article*].

⁴ See *infra* notes 104–112 and accompanying text.

curtailed enforcement of federal law against the medical use of cannabis in states that permit it, initially as a matter of Justice Department policy⁵ and later in the terms of legislative appropriations bills restricting permissible use of funds.⁶ As a result, in an expanding quasi-legal zone of state authorization and federal nonenforcement, doctors are recommending and patients are using cannabis products for medical treatment purposes in the U.S.⁷ Current federal law may thus be more effective at deterring medical cannabis research than it is at deterring non-research medical use.

The U.S. Food and Drug Administration (FDA) has approved a handful of natural and synthetic cannabinoid medications that contain chemical constituents found in cannabis over the past four decades. FDA recently approved Epidiolex—a solution of cannabidiol (CBD) derived from cannabis—for seizures associated with two rare and severe forms of epilepsy.⁸ However, FDA has not approved any non-purified cannabis⁹ plant material used under color of state medical cannabis laws, and it would

⁵ Memorandum for Selected United States Attorneys from David W. Ogden, Deputy Att’y Gen., on Investigations and Prosecutions in States Authorizing the Medical Use of Marijuana (Oct. 19, 2009) (“Ogden Memo”), [<https://perma.cc/BDD7-X66N>]; Memorandum for All United States Attorneys from James M. Cole, Deputy Att’y Gen. on Guidance Regarding Marijuana Enforcement (Aug. 29, 2013) (“Cole Memo”), <https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf> [<https://perma.cc/CYF5-DEC6>]. These memoranda from the prior administration were revoked by Attorney General Jefferson B. Sessions. Memorandum for All United States Attorneys from Jefferson B. Sessions III, Att’y Gen., on Marijuana Enforcement (Jan. 4, 2018), <https://www.justice.gov/opa/press-release/file/1022196/download> [<https://perma.cc/T2QN-4NY3>].

⁶ See, e.g., Consolidated Appropriations Act, 2018, Pub. L. 115-141, 132 Stat. 348 Div. B, Title V, § 538 (Mar. 23, 2018) (“None of the funds made available under this Act to the Department of Justice may be used, with respect to any of the States of Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming, or with respect to the District of Columbia, Guam, or Puerto Rico, to prevent any of them from implementing their own laws that authorize the use, distribution, possession, or cultivation of medical marijuana.”) This and similar riders have become known as the Rohrabacher-Blumenauer Amendment. Courts have relied on these provisions to prevent the Department of Justice from enforcing federal laws against uses of medical cannabis that comply with state medical cannabis laws. *E.g.*, *U.S. v. Marin Alliance for Medical Marijuana*, 139 F. Supp. 3d 1039 (N.D. Cal. 2015).

⁷ Wilson M. Compton et al., *Use of Marijuana for Medical Purposes in the United States*, 317 J. AM. MED. ASS’N. 209 (2017).

⁸ U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION, EPIDIOLEX (June 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/2103651bl.pdf [<https://perma.cc/VEY4-C4DL>].

⁹ For the most part we use the term “cannabis” in text rather than the term “marijuana” (or “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). However, when discussing a source that uses a different term, we sometimes conform our usage to that of the source in the interest of clarity. The CSA defines “marihuana” as follows:

The term “marihuana” means all parts of the plant *Cannabis sativa* 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 stalks, 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.

be difficult to demonstrate the safety and efficacy required for approval for these non-purified cannabis products under the federal Food, Drug and Cosmetic Act (FDCA).¹⁰

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.”¹¹

The CSA and the FDCA present distinct but interrelated obstacles to studying the effects of cannabis (and other Schedule I substances) in human patients.

It is a criminal offense to manufacture or distribute any Schedule I controlled substance without a license from the DEA.¹² 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).¹³ Although DEA announced in 2016 that, in principle, it was willing to register additional suppliers to provide cannabis to researchers, at the same time it signaled doubt about the eligibility for registration of suppliers who have previously violated the CSA—including through activity permitted under state law.¹⁴ If DEA considers such suppliers ineligible for registration, it follows 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 only products from registered suppliers—which for now means they must use the NCNPR-NIDA product.

In addition to requiring a DEA license, clinical studies of cannabis (as an unapproved drug) in humans would also require filing an investigational new drug application (IND) with FDA.¹⁵ Until recently DEA required an additional approval of the study protocol by NIDA, but since 2016, it has accepted FDA approval of the IND as adequate to ensure scientific merit of the study.¹⁶ Although some researchers have conducted small studies of cannabis products under INDs,¹⁷ FDA has only approved new drug applications (NDAs) for purified and synthetic cannabinoid products, and repeated petitions to DEA to reschedule cannabis plant material more broadly have so far failed.

21 U.S.C. § 802(16) (2018).

¹⁰ Codified as amended at 21 U.S.C. § 301 et seq. For an analysis of the obstacles to the development and approval of psychedelic drugs under current law, see Edward M. Sellers & Deborah B. Leiderman, *Psychedelic Drugs as Therapeutics: No Illusions About the Challenges*, 103 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 561–564 (2018).

¹¹ 21 U.S.C. § 812(b)(1)(B) (2018).

¹² 21 U.S.C. § 822(a)(1) (2018).

¹³ U.S. DEP’T. OF JUST., DRUG ENF’T ADMIN., Lyle E. Craker – Denial of Application, 74 Fed. Reg. 2101–2133 (Jan. 14, 2009) (hereinafter *Craker Denial*).

¹⁴ See *infra* notes 104–113 and accompanying text.

¹⁵ 21 U.S.C. § 355(i) (2018); 21 C.F.R. Part 312 (2018).

¹⁶ See *infra* note 110 and accompanying text; Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999, 80 Fed. Reg. 35960 (June 23, 2015).

¹⁷ See *infra* note 103.

Nonetheless, medical use of cannabis appears to be expanding in the U.S. Although some purported medical use may be recreational use in camouflage, some of it represents good faith efforts to provide health care for patients. In 2016, the Federation of State Medical Boards issued Model Guidelines for the Recommendation of Marijuana in Patient Care.¹⁸ 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.¹⁹ But the attitudes and practices of treating physicians and guidelines of state medical boards are not the measure of “currently accepted medical use in treatment in the United States” under the CSA as that language has been interpreted by the courts and agencies that administer U.S. drug laws.

The legal and political environment for medical cannabis has changed considerably since Congress passed the CSA in 1970. That 34 states (plus the District of Columbia, Guam, and Puerto Rico) have sought to make medical use of cannabis lawful within their borders—generally through voter referenda—indicates considerable popular support within the U.S.

The international legal regime that led the U.S. to pass the CSA shows similar signs of softening towards medical use of cannabis. The CSA brought US law into compliance with international treaties that require member states to control cannabis, and DEA cites these treaties in support of its regulatory moves. But some 30 other countries, including many member states of the treaties that require control of cannabis, now permit medical use of cannabis under their national laws.²⁰ Since 2018, the law of Canada has permitted recreational use of cannabis.²¹ The World Health Organization (WHO) convened 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” and has recommended less stringent regulation of cannabis and cannabis-derived products under international treaties.²²

The role of FDA in approving new medical technologies for clinical use has also evolved in the decades since longstanding interpretations of CSA standards for “currently accepted medical use” were put in place.²³ U.S. federal statutory standards

¹⁸ *Guidelines for the Recommendation of Marijuana in Patient Care*, FED’N OF STATE MED. BDS. (2016), <https://www.fsmb.org/globalassets/advocacy/policies/model-guidelines-for-the-recommendation-of-marijuana-in-patient-care.pdf> [<https://perma.cc/369B-8KWQ>].

¹⁹ Jonathan E. Adler & James E. Colbert, *Medicinal Use of Marijuana—Polling Results*, N. ENG. J. MED. Online (May 30, 2013), <https://www.nejm.org/doi/full/10.1056/NEJMc1305159> [<https://perma.cc/MX8D-ZFSJ>].

²⁰ See *Williams Motley Article*, *supra* note 3; *CND Intersessional 25 June 2018*, CND BLOG (June 25, 2018), <http://cnblog.org/2018/06/cnd-intersessional-25-june-2018/> [<https://perma.cc/U8UG-U7E7>] (explaining, some nations have gone further, including Canada, which recently decriminalized recreational use of cannabis with only muted response from other parties to the international agreements it is now violating).

²¹ Cannabis Act, S.C. 2018, c.16 (2018), <https://www.canlii.org/en/ca/laws/stat/sc-2018-c-16/latest/sc-2018-c-16.html> [<https://perma.cc/H2MS-XYTP>].

²² See Letter from Tedros Adhanom Ghebreyesus to Antonio Guterres (Jan. 24 2019), https://www.who.int/medicines/access/controlled-substances/UNSG_letter_ECDD41_recommendations_cannabis_24Jan19.pdf?ua=1 [<https://perma.cc/Q2MD-LY6Y>].

²³ See *infra* Section IV; see also Rebecca S. Eisenberg, *Shifting Institutional Roles in Biomedical Innovation in a Learning Healthcare System*, 14 J. INST’L ECON. 1139 at 1146–1150 (2018); W. Nicholson Price II, *Drug Approval in a Learning Health System*, 102 MINN. L. REV. 2413 at 2421–2426 (2018); Anna

for showing safety and efficacy for new drugs have not changed explicitly.²⁴ However, more recent statutory provisions have nudged FDA towards earlier initial approval for an expanding list of products while monitoring future data from ongoing studies and postapproval “real world evidence” after products have entered clinical use. Many medical devices and dietary supplements may be marketed with little or no premarket clinical testing.²⁵

A stunning recent example is the federal Right to Try Act of 2017,²⁶ which authorizes sponsors of new drugs to provide some patients with access outside of formal clinical trials to investigational drugs that remain in development following completion of Phase I trials. Although FDA previously authorized limited access to products in development under its “compassionate use” regulations,²⁷ the new legislation sends a clear signal to FDA that Congress may be ready to expand patient access to investigational drugs for which studies to date do not yet satisfy FDA approval standards.

Considered together, these developments raise questions about the political durability of the current regime and provide alternative models of regulatory and legal mechanisms to encourage research into the safety and effectiveness of cannabis products already in community and clinical use. Standards that FDA has used successfully to motivate the pharmaceutical industry to conduct rigorous premarket trials of proprietary new chemical entities may set impossible barriers to the study of cannabis products. Impossible barriers may be tolerable to law enforcement authorities whose primary concern is avoiding the harms caused by historically illegal drugs and the illicit drug market. They do little, however, to encourage the development of better data on the effects of cannabis products in patients, particularly by firms that already sell their products in the quasi-legal zone in states that purport to authorize medical use of cannabis. The paradoxical result could be to discourage the cannabis industry from investing in data collection, leaving doctors and patients with less information to guide use of medical cannabis products rather than more.

Congress is considering bills that would enlarge the autonomy of states to permit medical use of cannabis free of federal prohibitions.²⁸ But federal regulation may be necessary to promote meaningful studies of the effects of cannabis products in patients. State regulators lack the experience, expertise, and reputation of FDA in

B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305 at 332–41 (2011).

²⁴ These standards are summarized *infra* at notes 51–58 and accompanying text.

²⁵ See *infra* notes 155–164 and accompanying text (devices); *infra* notes 125–135 and accompanying text (supplements).

²⁶ Act of Mar. 30, 2018, Pub. L. No. 115-176, 132 Stat. 1372 (codified at 21 U.S.C. § 360bbb-0a).

²⁷ 21 C.F.R. § 312.1 (2019); 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> [<https://perma.cc/GZD6-LQDQ>].

²⁸ 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 [<https://perma.cc/4UYP-WFFL>].

evaluating drugs for safety and effectiveness.²⁹ Moreover, larger studies designed to meet the standards of a single federal regulator may be more informative and cost-effective than multiple smaller studies designed to meet the different standards of different state regulators. A modified federal regulatory regime might, therefore, do more than deference to state laws to promote studies and to provide information to guide more appropriate use of these products. In other contexts where strict premarket approval standards threaten to impose unsustainable research burdens on continued provision of products that enjoy political support, Congress has sometimes adapted the federal regime to make it more workable and less burdensome, while still providing for more limited data collection and FDA oversight.³⁰

Section I begins with a brief review of the key features of the current governing law, including the international Single Convention on Narcotic Drugs (Single Convention), 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 products, including burdens imposed on the use of Schedule I controlled substances in research, challenges to obtaining approval of botanical products, and substantial evidence of abuse potential and side effects generated over decades of government-funded research. Section IV reviews statutory and regulatory changes to FDA oversight of new medical technologies in the years since the passage of the CSA and considers possible regulatory adaptations that might lead to better information about the effects of medical cannabis products.

I. REGULATING CANNABIS UNDER THE SINGLE CONVENTION, THE CSA, AND THE FDCA

The most important of the international agreements requiring control of cannabis (among other substances) is the 1961 Single Convention on Narcotic Drugs (Single Convention).³¹ The Single Convention requires member states to restrict the use of controlled substances to medical and scientific requirements through controls on production, manufacture, distribution, and possession. But the Single Convention does not define “medical and scientific purposes,”³² and United Nations commentary

²⁹ Perhaps this is why, in new legislation providing for shared authority between the U.S. Department of Agriculture and the states to regulate production of “hemp” (defined as cannabis that contains less than 0.3% THC), Congress specified that it did not intend to affect or modify the authority of the FDA or HHS under the FDCA. Agriculture Improvement Act of 2018, Pub. L. 115-334, § 10113 (2018).

³⁰ See, e.g., 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.).

³¹ Single Convention on Narcotic Drugs, *opened for signature* Mar. 30, 1961, 18 U.S.T. 1407, 30 T.I.A.S. No. 6298, 520 U.N.T.S. 151, as amended (“Single Convention”).

³² See Single Convention, *supra* note 32, Art. 4(c):

“The parties shall take such legislative and administrative measures as may be necessary:
... (c) ... to limit exclusively to medical and scientific purposes the production,
manufacture, export, import, distribution of trade in, use and possession of drugs”

recognizes that national laws of member states may ascribe different meanings to those terms at different times.³³

The U.S., after initially holding out for stricter international controls, finally ratified the Single Convention in 1967, six years after it was opened for signature.³⁴ Congress passed the Controlled Substances Act of 1970 (CSA) three years later.³⁵ Consistent with the Single Convention, the CSA gives authority to the Attorney General (delegated to the DEA) to regulate the availability of drugs and substances of abuse to the quantities necessary for medical and scientific purposes by maintaining control over authorized manufacture and distribution and attempting to prevent diversion for recreational use and abuse.³⁶ But the CSA, like the Single Convention, left medical and scientific purposes undefined.

The provisions of the CSA³⁷ reflect compromise among competing priorities of law enforcement, medical and scientific use, treaty compliance, and public health. As a result, the meaning of the CSA has been contested from the start, with the scheduling of cannabis providing a recurring focus of legal challenges.³⁸

The CSA provides a taxonomy that sorts drugs or other substances into five different schedules with different levels of controls and penalties.³⁹ Congress specified initial lists of substances within each schedule⁴⁰ and established a process for adding new substances or rescheduling or descheduling substances according to statutory criteria.⁴¹ Congress placed cannabis in Schedule I,⁴² the most restrictive classification, reserved for drugs meeting three statutory requirements:

- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has no currently accepted medical use in treatment in the United States.

³³ United Nations, Commentary on the Single Convention on Narcotic Drugs, 1961 (1973) at 111 (Commentary on Art. 4, ¶¶11, 12) (“The term ‘medical purposes’ has not been uniformly interpreted by governments when applying the provisions of narcotics treaties containing it The term ‘medical purposes’ does not necessarily have exactly the same meaning at all times and under all circumstances. Its interpretation must depend on the stage of medical science at the particular time in question, and not only modern medicine . . . but also legitimate systems of indigenous medicine, such as those which exist in China, India and Pakistan, may be taken into account in this connexion.”)

³⁴ Cohrsen & Hoover, *supra* note 2, at 85–87.

³⁵ Act of Oct. 27, 1970, Pub. L. 91-513, 84 Stat. 1242 (codified as amended at 21 U.S.C. §§ 801 et seq).

³⁶ Cohrsen & Hoover, *supra* note 2, at 88-91.

³⁷ For a fuller discussion of the application of the CSA to cannabis, see Sean M. O’Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even After Descheduling*, 68 AM. U. L. R. 823 (2019) at Section II, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3242870 [<https://perma.cc/S9BS-W76U>] [hereinafter *O’Connor & Lietzan*].

³⁸ *Americans for Safe Access v. Drug Enf’t Admin.*, 706 F.3d 438 (D.C. Cir. 2013); *Gettman v. Drug Enf’t Admin.*, 290 F.3d 430 (D.C. Cir. 2002); *Alliance for Cannabis Therapeutics v. Drug Enf’t Admin.*, 15 F.3d 1131 (D.C. Cir. 1994); *Nat’l Org. for Reform of Marijuana Laws (NORML) v. Drug Enf’t Admin.*, 559 F.2d 735 (D.C. Cir. 1977).

³⁹ 21 U.S.C. § 812(b)(1)–(5) (2018).

⁴⁰ 21 U.S.C. § 812(c) (2018).

⁴¹ 21 U.S.C. §§ 811, 812 (2018).

⁴² 21 U.S.C. § 812(c) Schedule I (c)(10) (2018).

(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.⁴³

Schedules II, III, IV, and V are progressively less restrictive. Although they differ in their specified criteria for potential for abuse and the public health consequences of abuse or dependence, by definition Schedule II-V drugs and substances have a “currently accepted medical use in treatment in the United States.”⁴⁴

The CSA gives authority to the Attorney General⁴⁵ to add or remove drugs from the established schedules under a process that takes into account both treaty requirements and the evaluation of the Secretary of Health and Human Services (Secretary).⁴⁶ The Attorney General may initiate such proceedings on his motion, at the request of the Secretary, or on the petition of any interested party.⁴⁷ But first the Attorney General must request from the Secretary “a scientific and medical evaluation, and his recommendations, as to whether such drug or other substance should be controlled or removed as a controlled substance” based on a list of statutory factors.⁴⁸ The recommendations of the Secretary “shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance.”⁴⁹ The apparent reach of this language may be constrained by another statutory provision that allows the Attorney General to set these requirements aside as necessary to conform scheduling decisions to requirements for control of a substance under international treaties:

If control is required by United States obligations under international treaties, conventions, or protocols in effect on October 27, 1970, the Attorney General shall issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the [otherwise required statutory findings and procedures].⁵⁰

These statutory provisions and related administrative regulations have set the ground rules for repeated conflicts over the scheduling of cannabis, testing their limits in the courts.

⁴³ 21 U.S.C. § 812(b)(1) (2018).

⁴⁴ 21 U.S.C. §§ 812(b)(2)(B), 812(b)(3)(B), 812(b)(4)(B), 812(b)(5)(B) (2018).

⁴⁵ The Attorney General has in turn delegated this authority to the Administrator of the Drug Enforcement Administration or DEA. 28 C.F.R. § 0.100(b) (2003).

⁴⁶ The Secretary has in turn delegated this authority to the Commissioner of the Food & Drug Administration or FDA). U.S. Food & Drug Admin., Memorandum of Understanding with the Nat’l Inst. On Drug Abuse, 50 Fed. Reg. 9518 (Mar. 5, 1985); FDA Staff Manual Guide Vol. II – Delegations of Authority, SMG 1410.10 (Aug. 26, 2016).

⁴⁷ 21 U.S.C. § 811(a) (2018).

⁴⁸ 21 U.S.C. § 811(b) (2018). The statute requires the Secretary to consider scientific evidence of the pharmacological effect of the drug or substance, if known, the state of current scientific knowledge regarding the drug or other substance, what, if any, risk there is to the public health, its psychic or physiological dependence liability, whether the substance is an immediate precursor of a substance already controlled under this subchapter, as well as any “scientific and medical considerations involved in” other statutory factors including actual or relative potential for abuse, history and current pattern of abuse, and the scope, duration, and significance of abuse. 21 U.S.C. §§ 811(b), (c)(1)–(8) (2018).

⁴⁹ 21 U.S.C. § 811(b) (2018).

⁵⁰ 21 U.S.C. § 811(d)(1) (2018).

The FDCA sets distinct ground rules for a separate and much older legal regime that prohibits the introduction of any “new drug” into interstate commerce without FDA approval.⁵¹ This regime gives FDA considerable authority to restrict the use of cannabis for research as well as for medical purposes,⁵² in addition to its role in advising the Attorney General under the CSA. The apparent limitation of this authority to “new” drugs is illusory; the statute defines “new drug” as any drug that because of its composition “is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs” for use as described in the product label.⁵³ The courts have upheld FDA’s interpretation that this definition in effect requires both “old” and “new” drugs (as ordinary English speakers use those terms) to meet FDA standards for safety and effectiveness.⁵⁴

FDA regulates all aspects of the development, investigation, labeling, manufacture and postmarket surveillance of drug products and devices in the U.S. The Center for Drug Evaluation and Research (CDER) within FDA has an established process that governs the study, investigation, and manufacture of new drug products prior to product approval and marketing. For a new drug to be marketed lawfully in interstate commerce, FDA approval of a New Drug Application (NDA) must be in effect.⁵⁵ Such approval requires 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.”⁵⁶ Before conducting the human clinical trials necessary to meet this standard, the sponsor of the product must submit an IND to FDA. The IND submission must include data on the chemical structure, composition, pharmacology, and *in vitro* and animal toxicology studies, as well as a proposed protocol for initial study of the drug in humans.⁵⁷ Only if FDA accepts the IND may the sponsor begin testing the investigational drug in humans. During the conduct of the IND studies, drug sponsors must promptly report significant new safety information, including all known deaths and life-threatening events, to FDA. If at any point during the IND phase FDA determines that the drug represents an unreasonable risk to research subjects, it has statutory authority to place development of the drug and studies on “clinical hold.”⁵⁸ Once a sponsor has completed all necessary preclinical and clinical studies, it may submit the data to FDA in an NDA. The NDA must contain: full reports of all preclinical and clinical studies, a full safety report that captures data on all patients exposed to the new drug, chemistry and pharmacology data, manufacturing information, and a proposed product label. The new drug’s manufacturing methods and controls must be adequate to preserve the drug identity, quality, and purity.

FDA approval standards thus dominate drug development research as well as the marketing of drugs for medical treatment.

⁵¹ 21 U.S.C. § 355, 21 CFR part 314.

⁵² For a fuller discussion of the application of the FDCA to medical cannabis see *O’Connor & Lietzan*, *supra* note 37, at Section III.

⁵³ 21 U.S.C. § 321(p) (2016).

⁵⁴ *U.S. v. 50 Boxes More or Less*, 909 F.2d 24 (1st Cir. 1990).

⁵⁵ 21 U.S.C. § 355(a), (b), (j) (2018).

⁵⁶ 21 U.S.C. § 355(b)(1)(A) (2018).

⁵⁷ 21 U.S.C. § 355(i) (2018); 21 CFR § 312 (2018).

⁵⁸ 21 U.S.C. § 355(i)(3)(B) (2018).

Under these standards, FDA has approved NDAs for purified and synthetic versions of products that are present in cannabis for particular medical indications. FDA approved NDAs for two drug products containing dronabinol, a synthetic version of Delta 9- THC (THC), for treatment of nausea and vomiting in patients receiving chemotherapy and for treatment of loss of appetite in patients with HIV/AIDS: Marinol⁵⁹ and Syndros.⁶⁰ Another FDA-approved product, Cesamet, contains the active ingredient nabilone, a synthetically-derived compound with a chemical structure similar to THC.⁶¹ These products remain controlled under the CSA, but as FDA-approved products with demonstrated medical benefit, they are no longer in Schedule I.⁶² Epidiolex, the recently approved cannabidiol (CBD) product that contains no THC,⁶³ was placed in Schedule V, the least restrictive of the CSA schedules, consistent with FDA's evaluation and recommendation based on its finding that it has a relatively low potential for abuse.⁶⁴

Due to public and industry perception of prolonged delays between FDA NDA approval and DEA scheduling actions, Congress set a deadline for DEA to act on scheduling recommendations for new drugs in 2015 amendments to the CSA.⁶⁵ When the Secretary recommends that a new drug be controlled in schedule II, III, IV, or V, the Attorney General must issue an interim final rule controlling the drug within ninety

⁵⁹ Marinol was initially approved in 1985 for treatment of nausea and vomiting in patients receiving chemotherapy. It later received supplemental approval for treatment of loss of appetite in patients with HIV/AIDS. U.S. FOOD & DRUG ADMIN., MARINOL LABEL, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf [<https://perma.cc/QV2C-EJKE>].

⁶⁰ Syndros is an oral solution of nabilone that was first approved in 2016. U.S. FOOD & DRUG ADMIN., SYNDROS APPROVAL DOCUMENTS, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205525Orig1s000Approv.pdf [<https://perma.cc/8SY2-L9EB>].

⁶¹ FDA first approved Cesamet in 1985. U.S. FOOD & DRUG ADMIN., CESAMET APPROVAL DOCUMENTS, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018677> [<https://perma.cc/EWF7-ASBD>] (last visited Mar. 17, 2019).

⁶² The proper scheduling of these products under the CSA depends on their potential for abuse and dependence. 21 U.S.C. § 812(b) (2018). Dronabinol was rescheduled from Schedule I to Schedule II in 1986, U.S. Dep't. of Justice, Drug Enf't Admin., Schedules of Controlled Substances: Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule I to Schedule II; Statement of Policy, 51 Fed. Reg. 17476 (May 13, 1986), and then again rescheduled to Schedule III in 1999. U.S. Dep't. of Justice, Drug Enf't Admin., Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule II to Schedule III, 64 Fed. Reg. 35928 (July 2, 1999). Oral solutions of dronabinol remain in Schedule II. 82 Fed. Reg. 55504 (Nov. 22, 2017). Cesamet is also in Schedule II.

⁶³ U.S. FOOD & DRUG ADMIN, EPIDIOLEX APPROVAL LETTER, https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/210365Orig1s000Ltr.pdf [<https://perma.cc/XHR4-E3VR>]; U.S. FOOD & DRUG ADMIN., EPIDIOLEX PRESCRIBING INFORMATION, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf [<https://perma.cc/P9XZ-RNSP>].

⁶⁴ Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol; Corresponding Change to Permit Requirements, 83 Fed. Reg. 48950 (Sept. 28, 2018) [hereinafter *CBD Rescheduling Order*]. CBD was approved for treatment of rare forms of epilepsy, and several other anticonvulsant drug products unrelated to cannabinoids approved over the past decade have similarly been placed in Schedule V. See Schedules of Controlled Substances: Placement of Lacosamide into Schedule V, 74 Fed. Reg. 23789 (May 21, 2009); Schedules of Controlled Substances: Placement of Pregabalin into Schedule V, 70 Fed. Reg. 43633 (July 28, 2005).

⁶⁵ Improving Regulatory Transparency for New Medical Therapies Act, Pub. L. 114-89 § 2(b), 129 Stat. 698, 700 (2015) (codified in pertinent part as amended at 21 U.S.C. § 811(j)(2018)).

days.⁶⁶ In rescheduling Epidiolex, DEA made a point of specifying that the CSA does not require DEA to consider FDA's evaluation and recommendation for scheduling products such as CBD that the Single Convention requires it to control, while conceding that FDA approval established a currently accepted medical use in treatment that required removal of the product from Schedule I.⁶⁷

These FDA approvals of medical uses for synthetic THC and a purified cannabis-derived CBD product have not led DEA to modify the scheduling of cannabis more broadly. Cannabis remains in Schedule I, as does "marihuana extract," defined in DEA regulations as "an extract containing one or more cannabinoids that has been derived from any plant of the genus *Cannabis*, other than the separated resin (whether crude or purified) obtained from the plant."⁶⁸

There seems to be little prospect that DEA would reschedule unapproved products (including cannabis plant material from which FDA-approved products might be extracted and purified) under current law. But Congress can change the rules – indeed, it recently amended the CSA to exclude "hemp" from the statutory definition of "marihuana" and to exclude "tetrahydrocannabinols in hemp," provided it contains less than 0.3% THC, from the statutory list of Schedule I substances.⁶⁹

FDA standards for approving new drugs under the FDCA and DEA standards for rescheduling drugs under the CSA are not identical, although they are related. DEA's interpretation of the statutory language "currently accepted medical use in treatment in the United States" reflects DEA's understanding of what Congress meant when it included those words in 1970 statutory language. That understanding, as expressed in DEA rulings, reflects the FDCA and FDA practices, refracted through a DEA lens that has arguably introduced some distortions.

II. "CURRENTLY ACCEPTED MEDICAL USE IN TREATMENT" IN THE CONTEXT OF PETITIONS TO RESCHEDULE CANNABIS

The relationship between FDA approval standards under the FDCA and DEA scheduling standards under the CSA has been a source of confusion over the years. The confusion reflects disagreement within Congress over how to divide authority between the Attorney General (whose authority is now delegated to DEA⁷⁰) and the Secretary of Health, Education and Welfare (now the Secretary of Health and Human

⁶⁶ *Id.*

⁶⁷ *CBD Rescheduling Order*, *supra* note 64, at 48951–48952. For the relevant language of the CSA, see *supra* note 48 and accompanying text. DEA's interpretation of the statute appears to contradict the ruling of the Court of Appeals for the D.C. Circuit in *NORML v. Ingersoll*, 497 F.2d 654 (D.C. Cir. 1974). See *infra* notes 74–77 and accompanying text. *Cf.* Letter from Director General Tedros Adhanom Ghebreyesus, World Health Org. to Antonio Guterres, Secretary-General of the United Nations (23 July 2018), *supra* note 22 (recommending that "preparations considered to be pure CBD should not be scheduled within the International Drug Conventions.").

⁶⁸ Establishment of a New Drug Code for Marihuana Extract, 81 Fed. Reg. 90194, 90195 ("[I]f it were possible to produce from the cannabis plant an extract that contained only CBD and no other cannabinoids, such an extract would fall within the new drug code [for cannabis extracts and therefore be on Schedule I]."). The "separated resin" referenced in text is also a Schedule I substance, but it falls within the definition of "marihuana" itself rather than under the newly created code for extracts.

⁶⁹ See Agriculture Improvement Act of 2018, Pub. L. 115-334, *supra* note 29, § 12619. The new legislation defines "hemp" as cannabis that contains less than 0.3% THC. *Id.* § 10113.

⁷⁰ See *supra* note 45.

Services, whose authority is delegated to FDA⁷¹). The final text of the statute gives the Attorney General substantial authority over scheduling decisions,⁷² but also requires the Attorney General to follow procedures that include requesting from the Secretary a scientific and medical evaluation.⁷³ As noted above, some statutory language states that, at least in some circumstances, the Secretary's evaluation is binding on the Attorney General, while, other language suggests that in some circumstances the Attorney General can ignore the Secretary's findings and other procedural requirements.⁷⁴

Another possible source of confusion may be changing views over time within DEA as to whether FDA is a welcome ally with a shared regulatory mission or a looming threat to DEA's authority and autonomy in regulating drugs of abuse.

At first, DEA sought unsuccessfully to minimize the role of FDA in scheduling decisions. The National Organization for the Reform of Marijuana Laws (NORML) filed the first petition to reschedule cannabis in 1972.⁷⁵ DEA initially argued that since the Single Convention requires control of cannabis, the CSA gives the Attorney General the authority to regulate it under whichever schedule it considers most appropriate without having to consult with the secretary of HHS or otherwise engage in the rulemaking and hearing processes specified in the statute.⁷⁶

The Court of Appeals for the D.C. Circuit rejected this argument on the ground that it is inconsistent with an "overarching congressional aim" to limit the Attorney General's authority to make scheduling judgments and to give "final say with respect to medical and scientific determinations" to the Secretary.⁷⁷ Under this reading of the statute, DEA (with authority delegated from the Attorney General) may disregard statutory scheduling criteria, procedures, and recommendations of the Secretary only to the extent necessary for treaty compliance. The court also rejected DEA's alternative argument that the statute requires maintaining cannabis in Schedule I because it has no "currently accepted medical use." The court explained that this narrow focus on only one of the statutory factors is inconsistent with the multi-factor analysis set forth in the statute, which also requires consideration of "potential for abuse and danger of dependence."⁷⁸ Finally, the court concluded that a brief and conclusory letter in the file from the Acting Assistant Secretary for Health stating that there was currently no accepted medical use and no approved NDA for cannabis was insufficient to meet the procedures required in the statute for consulting with the Secretary about the scientific and medical evidence relevant to a scheduling decision.⁷⁹

⁷¹ See *supra* note 46.

⁷² 21 U.S.C. § 811(a) (2015).

⁷³ 21 U.S.C. § 811(b) (2015).

⁷⁴ See *supra* notes 45–50 and accompanying text.

⁷⁵ NORML v. DEA, 559 F.2d 735 (D.C. Cir. 1977); NORML v. Ingersoll, 497 F.2d 654 (D.C. Cir. 1974).

⁷⁶ See text accompanying note 50 *supra* for statutory language.

⁷⁷ NORML v. DEA, 559 F.2d at 745, 746.

⁷⁸ *Id.* at 748. The degree of "potential for abuse" is a statutory criterion for each of the five schedules, 21 U.S.C. § 812(b)(2015), while the "scope, duration, and significance of abuse" is one of eight statutory factors for the Attorney General to consider in making findings with respect to scheduling or rescheduling decisions. 21 U.S.C. § 811(c)(5) (2015).

⁷⁹ NORML v. DEA, 559 F.2d at 749–50.

A later decision from the Court of Appeals for the First Circuit reiterated that FDA marketing approval is not synonymous with “currently accepted medical use” and “lack of accepted safety under medical supervision” within the meaning of the CSA.⁸⁰ That court set aside a DEA order placing a different drug (3,4-methylenedioxymethamphetamine, known as MDMA) in Schedule I, holding that DEA had improperly treated the absence of FDA approval as conclusive evidence for purposes of the CSA.⁸¹ On remand, DEA again reached the same conclusion under a new interpretation of the statute, announcing eight characteristics of a drug with an accepted medical use in treatment apart from FDA approval.⁸²

DEA applied its new eight-factor test to the still-pending petition to reschedule cannabis in a 1989 decision, concluding that cannabis had no currently accepted medical use and must, therefore, remain in Schedule I.⁸³ On appeal, the D.C. Circuit said that DEA’s interpretation of the statutory standards was “in the main acceptable,” but questioned the 4th, 5th, and 8th criteria (i.e., “general availability of the substance and information regarding the substance and its use,” “recognition of its clinical use in generally accepted pharmacopeia, medical references, journals or textbooks,” and “recognition and use of the substance by a substantial segment of the medical practitioners in the United States”) on the ground that it was impossible for a Schedule I substance to satisfy these criteria.⁸⁴

On remand, DEA replaced the eight-factor test with the following five-part test:

1. The drug’s chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.⁸⁵

The D.C. Circuit ultimately affirmed this test on appeal,⁸⁶ and DEA has continued to apply the same test since that time.⁸⁷

⁸⁰ *Grinspoon v. Drug Enf’t Admin.*, 828 F.2d 881 (1st Cir. 1987).

⁸¹ *Id.* at 891.

⁸² The eight characteristics were “scientifically determined and accepted knowledge of its chemistry; the toxicology and pharmacology of the substance in animals; establishment of its effectiveness in humans through scientifically designed clinical trials; general availability of the substance and information regarding the substance and its use; recognition of its clinical use in generally accepted pharmacopeia, medical references, journals or textbooks; specific indications for the treatment of recognized disorders; recognition of the use of the substance by organizations or associations of physicians; and recognition and use of the substance by a substantial segment of the medical practitioners in the United States.” U.S. Dep’t. of Justice, *Drug Enf’t Admin., Schedules of Controlled Substances; Scheduling of 3,4-Methylenedioxymethamphetamine (MDMA) Into Schedule I of the Controlled Substances Act; Remand*, 53 Fed. Reg. 5,156, 5,157–58 (Feb. 22, 1988).

⁸³ U.S. Dep’t of Justice, *Drug Enf’t Admin., Marijuana Scheduling Petition; Denial of Petition*, 54 Fed. Reg. 53,767-02, 53,768 (Dec. 29, 1989).

⁸⁴ *Alliance for Cannabis Therapeutics v. Drug Enf’t Admin.*, 930 F.2d 936, 937–38 (D.C. Cir. 1991).

⁸⁵ U.S. Dep’t of Justice, *Drug Enf’t Admin., Marijuana Scheduling Petition; Denial of Petition; Remand*, 57 Fed. Reg. 10,499, 10,504–06 (Mar. 26, 1992).

⁸⁶ *Alliance for Cannabis Therapeutics v. Drug Enf’t Admin.*, 15 F.3d 1131, 1133, 1135 (D.C. Cir. 1994).

⁸⁷ *Ams. for Safe Access v. Drug Enf’t Admin.*, 706 F.3d 438, 449 (D.C. Cir. 2013).

The 1992 DEA order explaining its test highlights the significance of FDA approval standards in its understanding of what Congress meant by “currently accepted medical use” in the language of the CSA. DEA’s decision relied heavily on the FDCA as evidence of what drugs Congress considered acceptable for medical use.⁸⁸ DEA noted that in its initial assignments of drugs to CSA schedules in the statute, Congress seemed to place NDA-approved drugs in Schedules II, III, IV and V, but not in Schedule I. While recognizing that the First Circuit had previously decided that “NDA approval is not the only method by which drugs can achieve Federal recognition as having medical uses,” DEA did not take this to mean that CSA standards differ from FDCA standards. Rather, DEA noted that the FDCA also permits marketing of some drugs without an approved NDA, including drugs that are generally recognized as safe and effective (GRASE) and some pre-1938 drugs that are sheltered from regulation under a grandfather clause in the statute.⁸⁹

The five-factor test, as elaborated by DEA purportedly reflects its understanding of FDA standards and practices and attempts to conform to those standards. In explaining each factor, the DEA cites judicial decisions and FDA regulations implementing the FDCA. For example, in explaining the first factor (that the drug’s chemistry must be known and reproducible), DEA notes: “To be GRASE [the standard FDA acronym for the FDCA standard “generally recognized as safe and effective”] or to receive NDA approval, a drug’s chemistry must be known and reproducible.”⁹⁰ In explaining the second (adequate safety studies) and third (adequate and well-controlled studies proving efficacy) factors, DEA reflects FDA’s practice of treating these two standards as “inextricably linked,” explaining that “[a] determination that a drug is ineffective is tantamount to a determination that it is unsafe.”⁹¹ In explaining the fourth factor (acceptance of qualified experts), DEA concluded that in drafting the CSA, Congress intended to accommodate both NDA-approved drugs (which are accepted by the experts at FDA and its advisory committees) and GRASE drugs (which are accepted by a consensus of experts outside FDA) as meeting the standard of “accepted medical use.”⁹² Finally, in explaining the fifth factor (scientific evidence must be widely available), although noting that the FDCA does not require publication of evidence supporting an NDA, DEA concluded that this factor should be clarified as applying only in the absence of NDA approval.⁹³ At each step in the analysis, DEA presents its

⁸⁸ U.S. Dep’t of Justice, Drug Enf’t Admin., Marijuana Scheduling Petition; Denial of Petition; Remand, 57 Fed. Reg. 10,499, 10,503 (Mar. 26, 1992) (“By 1969, Congress had developed detailed Federal statutory criteria under the FDCA to determine whether drugs are acceptable for medical use.”).

⁸⁹ *Id.* at 10,503–04. Grandfathered drugs are excluded from the definition of “new drug” under 21 U.S.C. § 321(p), thus exempting them from IND and NDA approval requirements. *See supra* note 53 and accompanying text.

⁹⁰ U.S. Dep’t of Justice, Drug Enf’t Admin., Marijuana Scheduling Petition; Denial of Petition; Remand, 57 Fed. Reg. 10,499, 10,504 (Mar. 26, 1992) (citing FDA regulations and judicial decisions). For a fuller consideration of the application of these provisions to medical cannabis, *see O’Connor & Lietzan, supra* note 37, at III.A.1.

⁹¹ *Id.* (citing *United States v. Rutherford*, 442 U.S. 544 (1979), which upheld FDA’s decision that the FDCA did not permit marketing of the unapproved anticancer drug Laetrile to cancer patients.).

⁹² U.S. Dep’t of Justice, Drug Enf’t Admin., Marijuana Scheduling Petition; Denial of Petition; Remand, 57 Fed. Reg. 10,499, 10,505 (Mar. 26, 1992).

⁹³ *Id.* at 10,505–06.

factors as mirroring the practices of FDA under the FDCA.⁹⁴ That DEA relied on similarity to FDA practices to explain its interpretation of the CSA suggests that, at least on remand from a reviewing court, DEA thought it would be prudent to conform its statutory interpretation to the practices and views of FDA.

Apart from the relevance of FDA standards and practices to DEA interpretations of the CSA, FDA has direct input into specific scheduling decisions. Before initiating proceedings to reschedule a substance, “the Attorney General” (who delegates such matters to DEA) must request a scientific and medical evaluation and scheduling recommendation from “the Secretary” (who delegates such matters to FDA),⁹⁵ although DEA takes the position that the CSA does not require it to follow or even seek such an evaluation and recommendation for substances that the U.S. is obliged to control under international agreements.⁹⁶ The CSA requires both the Secretary and the Attorney General to consider eight statutory factors in determining the appropriate schedule for a substance:

- (1) Its actual or relative potential for abuse.
- (2) Scientific evidence of its pharmacological effect, if known.
- (3) The state of current scientific knowledge regarding the drug or other substance.
- (4) Its history and current pattern of abuse.
- (5) The scope, duration, and significance of abuse.
- (6) What, if any, risk there is to the public health.
- (7) Its psychic or physiological dependence liability.
- (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.⁹⁷

The CSA also requires the Secretary to make a scheduling recommendation; as noted above, the statutory criteria for choosing the right schedule turn in part on whether a substance has a currently accepted medical use.⁹⁸ FDA (on behalf of the Secretary) must, therefore, provide its evaluation of whether a substance has a

⁹⁴ In fact, FDA approval practices over the years have sometimes been more flexible than the DEA five-factor test would suggest. For example, FDA has sometimes approved products without a known and reproducible chemistry. A notable example (although not a controlled substance) is the once widely prescribed hormone replacement drug Premarin, isolated from the urine of pregnant mares, which contains a mixture of more than 50 estrogens. See DEP'T OF HEALTH & HUMAN SERV., OFF. INSPECTOR GEN'L, REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S HANDLING OF ISSUES RELATED TO CONJUGATED ESTROGENS (May 16, 1997); Marcia L. Stefanich, *Estrogens and Progestins: Background and History, Trends in Use, and Guidelines and Regimens Approved by the U.S. Food and Drug Administration*, 118 (12B) AM. J. MED. 645-735 (2005). FDA has licensed many biological products with complex and incompletely defined structures produced in biological processes that cannot be reliably reproduced. FDA regulates these products for safety under the FDCA and for safety, purity and potency under the Public Health Service Act (PHSA), Public L. No. 115-271 (Oct. 24, 2018). DEA may have had its own regulatory reasons for including in its test of “currently accepted medical use” more rigorous requirements than FDA uses for new drug approvals.

⁹⁵ See *supra* notes 48–49 and accompanying text.

⁹⁶ See *supra* note 67 and accompanying text.

⁹⁷ 21 U.S.C. § 811(c) (2015).

⁹⁸ See *supra* notes 39–48 and accompanying text.

currently accepted medical use in the United States in order to make a scheduling recommendation. For this purpose, FDA analyses refer to the DEA's five-factor test,⁹⁹ because scheduling decisions are governed by the CSA (as interpreted by DEA and the courts), rather than the FDCA (as interpreted by FDA and the courts).

So far FDA has consistently recommended against rescheduling cannabis, and DEA has consistently concurred, most recently rejecting a petition from the governors of Rhode Island and Washington to initiate rescheduling proceedings.¹⁰⁰ But DEA also maintains that because the Single Convention obliges the U.S. to control cannabis, the DEA Administrator must control cannabis under the schedule that he deems most appropriate without regard to the findings required and procedures specified under section 811 of the CSA, suggesting that DEA might in the future disregard FDA rescheduling recommendations.¹⁰¹

Significant changes have occurred in the statutory language of the FDCA and the administrative practice of the FDA in approving a variety of products used for medical purposes in the years since passage of the CSA. We consider these changes and their implications for medical cannabis in Section IV below. But first, Section III considers obstacles to gaining FDA approval for cannabis arising in part from its Schedule I status.

III. SPECIAL OBSTACLES TO FDA APPROVAL OF CANNABIS

The most straightforward way to get around both the CSA and the FDCA for a medical cannabis product might seem to be to carry out the necessary research to establish its safety and effectiveness for a medical indication to the satisfaction of FDA and to submit an NDA.¹⁰² FDA has repeatedly noted the absence of an approved NDA for cannabis (broadly defined) in recommending to DEA that it maintain cannabis in Schedule I, and DEA has repeatedly cited this fact in denying rescheduling petitions.¹⁰³ But a sponsor seeking NDA approval for cannabis would face a number of obstacles beyond those confronting a small molecule drug.

One source of difficulty is that cannabis is already a Schedule I controlled substance. Schedule I classification comes with controls that make it especially burdensome to conduct research. It is a criminal offense to manufacture or dispense a Schedule I substance unless the manufacturer has registered with the Attorney

⁹⁹ U.S. Dep't. of Justice, Drug Enf't Admin., Schedule of Controlled Substances: Maintaining Marijuana in Schedule I of the Controlled Substances Act, Background, Data and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b), 81 Fed. Reg. 53,739, (Aug. 12, 2016).

¹⁰⁰ U.S. Dep't. of Justice, Drug Enf't Admin., Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 Fed. Reg. 53,688 (Aug. 12, 2016). *See also* U.S. Dep't. of Justice, Drug Enf't Admin., Denial of Petition to Initiate Proceedings to Reschedule Marijuana; Proposed Rule, 76 Fed. Reg. 40,552 (July 8, 2011).

¹⁰¹ U.S. Dep't. of Justice, Drug Enf't Admin., Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 Fed. Reg. at 53,688, 53,689 (Aug. 12, 2016); *See supra* note 67 and accompanying text.

¹⁰² For a fuller discussion of the requirements for an NDA for cannabis, *see O'Connor & Lietzan, supra* note 37, at III.A.2.

¹⁰³ FDA has reported to DEA that some human trials of cannabis have been conducted under FDA-regulated IND applications, 81 Fed. Reg. at 53700, but that no NDAs for cannabis have been approved apart from specific purified or synthetic cannabinoid products. U.S. Dep't. of Justice, Drug Enf't Admin., Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 Fed. 53,688, 53,700 (Aug. 12, 2016).

General.¹⁰⁴ The CSA directs the Attorney General to register applications “if he determines that such registration is consistent with the public interest and with United States obligations under international treaties.”¹⁰⁵ The statute provides a list of criteria to consider in determining the public interest, including

maintenance of effective controls against diversion . . . into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture . . . to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes . . .¹⁰⁶

DEA administration of the registration requirement has had the practical effect of preventing cannabis manufacturers from obtaining approval to study their own products in clinical trials. Researchers who wish to use “marijuana plant material” in their research may not grow their own cannabis or buy it from commercial growers but must procure it from NIDA.¹⁰⁷ Since 1968, the NCNPR has been the only registered manufacturer of cannabis for research purposes, operating under a contract administered by NIDA.¹⁰⁸ DEA has justified this restrictive approach on the ground that the risk of diversion increases with each new registered manufacturer.¹⁰⁹

In 2016, DEA announced steps to facilitate the registration of more growers to produce cannabis for research and to allow growers with prior written approval from DEA to supply cannabis directly to researchers without having to go through NIDA.¹¹⁰ But DEA understands its statutory obligation to restrict registration “consistent with the public interest” to argue against registration of growers who have ever provided cannabis in violation of federal law, even if the activity was permitted under state law:

. . . in determining whether the proposed registration would be consistent with the public interest, among the factors to be considered are . . . whether the applicant has engaged in illegal activity involving controlled substances. In this context, illegal activity includes any activity in

¹⁰⁴21 U.S.C. § 822(a) (2015).

¹⁰⁵21 U.S.C. § 823(a) (2015).

¹⁰⁶21 U.S.C. § 823(a)(1) (2015).

¹⁰⁷NAT’L INST. OF DRUG ABUSE, MARIJUANA PLANT MATERIAL AVAILABLE FROM THE NIDA DRUG SUPPLY PROGRAM (Mar. 2016), <https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program> [<https://perma.cc/5ZF7-6S4A>].

¹⁰⁸*Craker Denial*, *supra* note 13.

¹⁰⁹*Id.* at 2129.

¹¹⁰U.S. Dep’t. of Justice, Drug Enf’t Admin., Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States, 81 Fed. Reg. 53846–53848 (Aug. 12, 2016). DEA and HHS have further sought to liberalize the rules governing cannabis research by eliminating a previous requirement for Public Health Service (PHS) review of research protocols, in addition to FDA review of INDs. U.S. Dep’t. of Health & Human Serv., Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999, 80 Fed. Reg. 35960–35961. The prior policy may be found at <https://grants.nih.gov/grants/guide/notice-files/not99-091.html>.

violation of the CSA (regardless of whether such activity is permissible under State law)¹¹¹

This understanding poses a special obstacle for any firm currently supplying cannabis products for medical or other use that wishes to supply its own products for use in research. The perverse result is to exclude from registration the firms that might otherwise have the strongest interest in promoting cannabis research and to prevent clinical trials of most of the cannabis products that are actually used for medical purposes in the U.S. today.

As of this writing, DEA has not approved any additional registrations.¹¹² Nonetheless, DEA has proposed a five and a half fold increase in the aggregate production quota for cannabis (presumably the NCNPR/NIDA products) for use in research in 2019,¹¹³ suggesting increased demand from researchers. But research using NCNPR/NIDA cannabis products will likely provide less useful data for doctors and patients than research with the products they currently use for medical purposes, and will not support FDA approval of untested products.

Other significant challenges arise because cannabis is a plant with many active and inactive constituents that exhibits biological variability rather than an isolated or synthetic chemical entity that can be reliably reproduced. This makes it difficult both to meet FDA standards for an NDA and to satisfy DEA requirements for rescheduling.

Although many societies have used plants (including cannabis) for medicinal purposes since prehistoric times, the biological complexity and variability of plants present challenges for studying their effects with the scientific rigor that the FDCA requires for new drugs.¹¹⁴ FDA may refuse an application if it finds that 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 that “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.”¹¹⁵ The statute defines “substantial evidence” 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

¹¹¹ *Id.*

¹¹² According to an August 31, 2018 letter from a bipartisan group of 14 members of Congress to Attorney General Jefferson Sessions published in a blog post, <https://reason.com/assets/db/15363449387939.pdf> [<https://perma.cc/5GLZ-ZYHA>], 26 applications to manufacture marijuana for research use have been submitted to DEA and await decision.

¹¹³ U.S. Dep’t of Justice, Drug Enf’t Admin., Proposed Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2019, 83 Fed. Reg. 42164, 42167 (Aug. 20, 2018).

¹¹⁴ See Neha Arora Chugh, Shreya Bali & Ashwani Koul, *Integration of botanicals in contemporary medicine: road blocks, checkpoints and go-ahead signals*, 7 INTEGRATIVE MED. RES. 109, 109-25 (2018).

¹¹⁵ 21 U.S.C. § 355(d)(1), (5) (2015).

have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.¹¹⁶

As elaborated in FDA regulations,¹¹⁷ these standards ordinarily require data from randomized, controlled trials indicating that the active ingredient in the product is safe and effective for a particular medical indication. Although these standards apply to all drugs, designing clinical trials of cannabis to meet these standards presents serious challenges.¹¹⁸

In its most recent medical and scientific evaluation and recommendation regarding the scheduling of marijuana (broadly defined to include all cannabis cultivated strains) in 2016,¹¹⁹ FDA repeatedly noted that marijuana has hundreds of different natural constituents that vary between strains, that marijuana products from different strains will have different safety, biological, pharmacological, and toxicological profiles, that the concentrations of different constituents may vary even within a strain depending on growing conditions and processing, and that these variations prevent the use of consistent standardized doses and therefore complicate interpretation of clinical data from trials using marijuana.¹²⁰ This suggests that cannabis (broadly defined) lacks the “known and reproducible chemistry” that DEA looks for to establish “currently accepted medical use,” although FDA suggested that “if a specific cannabis strain is grown and processed under strictly controlled conditions, the plant chemistry may be kept consistent enough to produce reproducible and standardized doses.”¹²¹ Another problem that FDA noted is that “smoking marijuana currently has not been shown to allow delivery of consistent and reproducible doses,”¹²² although other routes of administration could potentially avoid this problem. Finally, although similar challenges arise in studying other drugs active in the central nervous system such as anxiolytics, sedative-hypnotics, opioid analgesics, and certain anticonvulsants, there are challenges to designing and conducting blinded, placebo-controlled trials for substances with well-recognized subjective psychoactive effects.¹²³

Some of these challenges would arise in studying the effects of other plants that many people consume in the U.S. for health purposes, including herbal remedies such as Echinacea, ginkgo biloba, St. John’s wort, and ginseng, if those products required

¹¹⁶21 U.S.C. § 355(d) (2015).

¹¹⁷21 C.F.R. 314 (2018).

¹¹⁸FDA addresses some of these challenges on its website at <https://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm#expandedaccess> [<https://perma.cc/H76B-YBJF>] (archived on May 22, 2019).

¹¹⁹Reproduced in full at U.S. Dep’t of Justice, Drug Enf’t Admin., Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 Fed. Reg. 53688, 53689-53707.

¹²⁰81 Fed. Reg. at 53692 (consideration of “scientific evidence of its pharmacological effects, if known”), 53698-99 (consideration of “the state of current scientific knowledge regarding the drug or other substance”), 53700 (consideration of element of five-factor test for “currently accepted medical use” that “the drug’s chemistry much be known and reproducible.”

¹²¹*Id.* at 53700.

¹²²*Id.*

¹²³David Casarett, *The Achilles Heel of Medical Cannabis Research—Inadequate Blinding of Placebo-Controlled Trials*, 178 J. AM. MED. ASS’N. INTERN. MED. 9, 9–10 (2018); Edward M. Sellers, Myroslava K. Romach, & Deborah B. Leiderman, *Studies with Psychedelic Drugs in Human Volunteers*, 142 NEUROPHARMACOLOGY 116, 116–34 (2018). For a fuller discussion of this issue see O’Connor & Lietzan, *supra* note 37, at III.2.b.–c.

FDA approval.¹²⁴ Many patients use these products to treat disease in the belief that they are safe and effective, although without the benefit of rigorous studies. But different political forces have created a very different legal and regulatory environment for these products than for cannabis. Congress has constrained FDA's ability to regulate these products under its usual rules for either food¹²⁵ or drugs, carving out a new regulatory category of "dietary supplements"¹²⁶ under the Dietary Supplement Health and Education Act of 1994 (DSHEA).¹²⁷ Dietary supplements that have been on the market since 1994 may be sold for general health and nutrition purposes without FDA approval so long as they include a statutory disclaimer that FDA has not approved claims made for the product¹²⁸ and they do not claim to be useful in diagnosing, treating, curing, or preventing disease.¹²⁹ Rather than requiring manufacturers to show safety and effectiveness prior to marketing these products, the statute places the burden on FDA to show that the products present an unreasonable risk of illness or injury in order to remove them from the market.¹³⁰

Manufacturers or distributors of new dietary ingredients introduced after October 15, 1994 must submit a premarket safety notification to FDA at least seventy-five days prior to introducing it into commerce providing information indicating why a dietary

¹²⁴Robert J. Blendon et al., *Americans' Views on the Use and Regulation of Dietary Supplements*, 161 ARCH. INTERN. MED. 805 (2001), <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm053843.htm> [<https://perma.cc/ZVD7-DB7W>].

¹²⁵The Nutrition Labeling and Education Act of 1990, Pub. L. No. 101-535, 104 Stat. 2353, gave FDA new authority to promulgate requirements for nutritional labeling in food products and delegated authority to FDA to establish criteria for making claims about health benefits. Two years later, Congress temporarily blocked FDA from applying its new labeling requirements for conventional foods to vitamins, minerals, herbs, and similar nutritional substances. Dietary Supplement Act of 1992, Pub. L. No. 102-571.

¹²⁶The statute defines "dietary supplement" as "(1) a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E); (2) a product that (a)(I) is intended for ingestion . . . (ii) [complies with statutory requirements]; (B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and (C) is labeled as a dietary supplement; and (3) [certain products that have been approved as drugs but were previously sold as dietary supplements]". 21 U.S.C. § 321(ff) (2015).

¹²⁷Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified as amended in scattered provisions of 21 U.S.C.)

¹²⁸The statute permits manufacturers of dietary supplements to make certain claims of benefit for their products "related to a classical nutrient deficiency disease" if the manufacturer "has substantiation that such statement is truthful and not misleading" and if the statement contains the following disclaimer:

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.

21 U.S.C. § 343(r)(6)(A)–(C) (2015).

¹²⁹21 U.S.C. § 343(r)(6)(C) (2015). "Health claims" that the product prevents disease are permissible, but "treatment claims" are not. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FDA'S IMPLEMENTATION OF "QUALIFIED HEALTH CLAIMS": QUESTIONS AND ANSWERS; FINAL GUIDANCE (May 12, 2006), <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm053843.htm> [<https://perma.cc/JU4E-ENEf>].

¹³⁰21 U.S.C. § 342(f)(1) (2015). FDA used this authority to prevail on appeal against the dietary supplement Ephedra, used for weight loss, after compiling an extensive administrative record over a period of years that it was killing people. *Nutraceutical Corp. v. Von Eschenbach*, 459 F.3d 1033 (10th Cir. 2006). But other efforts to regulate dietary supplements have been less successful.

supplement containing the ingredient is reasonably expected to be safe.¹³¹ Such a submission is not necessary for dietary ingredients “which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.”¹³²

Only if manufacturers wish to market their products explicitly for the diagnosis, treatment, cure, or prevention of disease must they go through the full rigors of the FDA new drug application process.¹³³ From the perspective of supplement manufacturers, this is a costly and risky effort for products that they are otherwise free to market (albeit with restrictions on permissible claims) under the DSHEA.¹³⁴ But the relatively relaxed standards for dietary supplements have had adverse consequences for public health.¹³⁵

Perhaps hoping to encourage more firms to study the health effects of products that might otherwise be sold as dietary supplements and to submit data for regulatory review, FDA has sought to clarify and make more flexible the path to FDA approval for botanical drugs. FDA created a Botanical Review Team “to help manage the unique features and review issues associated with botanical drug products” and to act “as an advisory resource” for regulators.¹³⁶ FDA first published guidance for industry on the development of botanical drugs in 2004 and updated this guidance in 2016 in light of experience.¹³⁷ This guidance offers strategies for achieving consistent therapeutic results given “the heterogeneous nature of a botanical drug and possible uncertainty about its active constituents.”¹³⁸ FDA suggests that clinical trials should use botanical raw material control (i.e., control of agricultural practice and collection), chemical tests that capture the active or chemical constituents of a botanical drug substance, manufacturing control (i.e., control of the manufacturing process), and

¹³¹21 U.S.C. § 350B(a)(2) (2015). FDA has specified recommended content for such a notification in a detailed draft guidance document. See CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, U.S. FOOD & DRUG ADMIN., DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENTS NOTIFICATIONS AND RELATED ISSUES: DRAFT GUIDANCE FOR INDUSTRY (Aug. 2016).

¹³²21 U.S.C. § 350b(a)(1) (2015).

¹³³21 U.S.C. § 343(r)(6) (2015) (allowing certain claims about benefits of dietary supplements to be made only with a prominent boldface disclaimer that “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.”); Certain Types of Statements for Dietary Supplements, 21 C.F.R. § 101.93(c) (2016); U.S. Food & Drug Admin., Food Labeling; Requirements for Nutrient Content Claims; Health Claims; and Statements of Nutritional Support for Dietary Supplements, 62 Fed. Reg. 49859 at 49860-49861 (Sept. 23, 1997).

¹³⁴A number of obstacles would complicate use of the DSHEA for medical cannabis, including a statutory exclusion from the definition of “dietary supplement” for any article that was approved or authorized for investigation as a new drug or biologic unless it was previously marketed as a dietary supplement. 21 U.S.C. § 321(ff)(3) (2015). For a careful analysis of the implications for cannabis under current law, see O’Connell & Lietzan, *supra* note 37, at III.C.

¹³⁵Colin W. Binns et al., *Problems and Prospects: Public Health Regulation of Dietary Supplements*, 39 ANN. REV. PUB. HEALTH 403, 412–13 (2018).

¹³⁶U.S. FOOD & DRUG ADMIN., CENTER FOR DRUG EVAL. & RESEARCH (CDER), MAPP 5210.9, REVIEW OF BOTANICAL DRUG PRODUCTS, 2 (2016), <https://www.fda.gov/media/72454/download> [<https://perma.cc/T7LC-JH7G>].

¹³⁷U.S. FOOD & DRUG ADMIN., CENTER FOR DRUG EVAL. & RESEARCH (CDER), BOTANICAL DRUG DEVELOPMENT GUIDANCE FOR INDUSTRY 1 (2016), <https://www.fda.gov/downloads/Drugs/Guidances/UCM458484.pdf> [<https://perma.cc/5W2Z-PVV3>].

¹³⁸*Id.* at 4.

biological assays that reflect the drug's known or intended mechanism of action. Some of these strategies may be useful for cannabis studies.¹³⁹

FDA has had few takers so far. Two NDAs for botanical prescription drug products have been approved to date: Veregen (sinecatechins), a topical ointment for treatment of genital and perianal warts that includes an extract of green tea leaves,¹⁴⁰ and Mytesi (crofelemer), a drug for the treatment of diarrhea in HIV/AIDS patients that includes an extract from the red bark sap of the *Croton lechleri* tree.¹⁴¹ The FDA approval documents reveal that these products spent years in a lengthy process of clinical trials and regulatory review, with the Botanical Review Team playing a critical role in encouraging the necessary flexibility to get these products approved.¹⁴² Meanwhile, millions of people use botanical dietary supplements in the U.S. to treat a variety of ailments without the benefit of FDA review of any data from clinical trials.¹⁴³

It is notable that both of these approved botanical drug products are proprietary products developed, studied, and approved in formulations that are unlikely to face competition from unapproved dietary supplements. These products have commercial sponsors that expect to profit from a period of market exclusivity. It would be much more challenging to motivate a firm to invest in rigorous clinical trials and to navigate a complex and uncertain regulatory approval process to sell as an FDA-approved "drug" a product that would immediately face competition from unapproved products that are widely available, whether from health food stores or from state-licensed cannabis dispensaries.

Cannabis faces another challenge that distinguishes it from other new drugs and from many dietary supplements. Both for FDA approval of an NDA and for DEA rescheduling based on a finding of "currently accepted medical use," evidence of effectiveness must be balanced against evidence of safety risks. For most new drugs, there is relatively little information available about either effectiveness or safety before the product sponsor begins research. Toxic side effects may emerge in clinical trials, but if they are rare relative to the size of the trial they may only show up in postapproval studies or adverse event reports in the course of clinical experience after the drug has reached the market.¹⁴⁴ By contrast, the U.S. government has been sponsoring studies of cannabis for decades, providing an extensive public record of its potential for abuse, psychoactive effects, behavioral impairment, and other side effects to weigh against new evidence of effectiveness in treatment.¹⁴⁵ A new drug that may

¹³⁹For a fuller consideration of this issue see *O'Connor & Lietzan, supra* note 37, at III.A.2.a.

¹⁴⁰U.S. FOOD & DRUG ADMIN., DRUG APPROVAL PACKAGE, VEREGEN OINTMENT (2006), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021902s000TOC.cfm [<https://perma.cc/PR83-862G>].

¹⁴¹CTR. FOR DRUG EVAL. & RESEARCH, APPLICATION NUMBER: 202292ORIG1S000, SUMMARY REVIEW (2012), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000SumR.pdf [<https://perma.cc/Y6NT-V6M9>].

¹⁴²See *O'Connor & Lietzan, supra* note 37, at III.A.2 at 869.

¹⁴³Ranjani R. Starr, *Too Little, Too Late: Ineffective Regulation of Dietary Supplements in the United States*, 105 AM. J. PUBLIC HEALTH 478, 478 (2015).

¹⁴⁴Nicholas S. Downing *et al.*, *Postmarket Safety Events Among Novel Therapeutics Approved by the U.S. Food & Drug Administration Between 2001 and 2010*, 317 J. AM. MED. ASS'N. 1854, 1867 (2017).

¹⁴⁵See, e.g., Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 81 Fed. Reg. 53688 at 53690–706 (Aug. 12, 2016) (reviewing extensive literature on abuse potential, pharmacological effects, association with psychosis, etc.).

prove in time to have comparable side effects to cannabis may thus be easier to get approved, because the bad news is not yet known at the time of approval. On the other hand, after many years of widespread use, some observers of the data might believe that, although inconclusive, the negative side effects of cannabis are not especially alarming relative to those of other widely used drugs.¹⁴⁶

The requirements for approval of an NDA aim to ensure that decisions rest on valid, reproducible science. Sometimes rigorous scientific requirements lead to better studies and better information.¹⁴⁷ This is often the case for lucrative proprietary pharmaceutical products that will be sold at premium prices.

However, in other cases, the result of more rigorous standards is not better information, but rather no information. If meeting regulatory standards is impossible, unlawful, or unaffordable, and if manufacturers are already able to distribute their products profitably without FDA approval and with little fear of federal law enforcement, rigorous standards may fail to generate new information. This may be the case for many medical cannabis products currently in use.

IV. MODIFIED APPROACHES FOR APPROVING AN EXPANDING SET OF MEDICAL TECHNOLOGIES

Decades before the modern evidence-based medicine movement,¹⁴⁸ FDA worked with academia, NIH, and industry scientists and physicians to develop rigorous standards for evaluating the safety and effectiveness of new drugs.¹⁴⁹ These standards bypassed the judgments of the medical profession, instead relying on new scientific disciplines, such as toxicology and clinical pharmacology, and incorporating new standards of assessment that required experimental protocols, use of controls, and randomization. Congress endorsed FDA's approach by adopting statutory standards that defined the necessary evidence for new drug approval from the perspective of "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."¹⁵⁰ The standards led to the removal of some products from the market, notwithstanding medical testimony that doctors considered them safe and effective.¹⁵¹

¹⁴⁶For an excellent review and discussion of the evidence concerning health effects of cannabis see NAT'L ACAD. OF SCIENCES, ENG., MEDICINE, & MED., *THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH* (2017).

¹⁴⁷For a fuller presentation of this argument see Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 385 (Nat'l Acads. Press. 2007).

¹⁴⁸See Evidence-Based Medicine Working Group, *Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine*, 268 J. AM. MED. ASS'N. 2420, 2420 (1992) ("A new paradigm for medical practice is emerging. Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature."); see generally Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373 (2002).

¹⁴⁹See Daniel Carpenter, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* 118–227 (2010); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1772 (1996).

¹⁵⁰21 U.S.C. § 355(d) (2018).

¹⁵¹*United States v. 50 Boxes More or Less*, 909 F.2d 24, 26 (1990).

These are the FDA standards that DEA concluded Congress had in mind in 1970 when it used the language “currently accepted medical use in treatment in the United States”¹⁵² in defining statutory criteria for scheduling controlled substances.¹⁵³ But since 1970, Congress has repeatedly revised the FDCA to permit a growing list of products to get to market more easily.¹⁵⁴

The statutory provisions for approval of medical devices,¹⁵⁵ which were added in the Medical Device Amendments Act of 1976,¹⁵⁶ direct FDA to rely less heavily on premarket testing, even for the relatively rare devices that require premarket approval.¹⁵⁷ In contrast to the more uniform and rigorous premarket review requirements for drugs, Congress adopted a risk-based stratified approach for medical devices that requires premarket approval for only the highest-risk (Class III) devices.¹⁵⁸ Even for Class III devices, the statute directs FDA to “consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.”¹⁵⁹ 1997 amendments added a “least burdensome provision” to the statute, mandating that FDA only request premarket clinical data that are “necessary to establish device effectiveness.”¹⁶⁰

These provisions challenge FDA to minimize reliance on premarket testing whenever it can instead approve new devices based on a preliminary premarket showing with provision for ongoing postmarket data collection.¹⁶¹ FDA has issued draft guidance on the use of “real-world data” collected outside of traditional trials for regulatory decision-making for devices, indicating when it considers such data to be of sufficient quality and reliability for regulatory purposes.¹⁶² Most new devices avoid even this limited premarket approval requirement by relying on a statutory provision that substitutes a less onerous premarket notification process known as the “510(k)

¹⁵²21 U.S.C. § 812(b)(1)(B) (2018).

¹⁵³See *supra* notes 85–90 and accompanying text.

¹⁵⁴These legislative adjustments generally leave FDA with considerable discretion to use its own judgment, and some observers argue that FDA has exercised this discretion conservatively to maintain high premarket approval standards in order to avoid harm to patients. *E.g.*, Laakman, *supra* note 23, at 316–17.

¹⁵⁵21 U.S.C. § 360(c)(2) (2017).

¹⁵⁶Medical Device Amendments Act of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976).

¹⁵⁷U.S. FOOD & DRUG ADMIN., CTR. FOR DEVICES & RADIOLOGICAL HEALTH, CTR. FOR BIOLOGICS EVAL. & RESEARCH, BALANCING PREMARKET AND POSTMARKET DATA COLLECTION FOR DEVICES SUBJECT TO PREMARKET APPROVAL: GUIDANCE FOR INDUSTRY AND FOOD & DRUG ADMINISTRATION STAFF (2015) (hereinafter FDA 2015 BALANCING PREMARKET AND POSTMARKET DATA).

¹⁵⁸Jordan Baumann, *The “Déjà vu Effect:” Evaluation of United States Medical Device Legislation, Regulation, and the Food and Drug Administration’s Contentious 510(k) Program*, 67 FOOD & DRUG L. J. 337, 342–61 (2012).

¹⁵⁹21 U.S.C. § 360c(a)(3)(C) (2012).

¹⁶⁰21 U.S.C. § 360c(a)(D)(ii) (2012).

¹⁶¹FDA 2015 BALANCING PREMARKET AND POSTMARKET DATA, *supra* note 157, at 6.

¹⁶²U.S. Dep’t of Health & Human Servs., Food & Drug Admin., CENTER FOR DEVICES & RADIOLOGICAL HEALTH, CENTER FOR BIOLOGICS EVALUATION & RESEARCH, USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (as updated Sept. 16, 2016) [hereinafter FDA 2016 REAL-WORLD EVIDENCE FOR DEVICES].

process”¹⁶³ for Class II devices, including new devices shown to be “substantially equivalent” to previously cleared Class II devices.¹⁶⁴

The less stringent premarket regulatory requirements make the imprimatur of FDA approval or clearance less meaningful for devices than for drugs,¹⁶⁵ but by lessening regulatory burdens, they make it possible for more firms to survive in an industry that often operates on lower profit margins than the pharmaceutical industry.¹⁶⁶

Another category of products that would likely not be cost-effective to provide if required to meet rigorous premarket approval requirements is compounded drugs. In traditional drug compounding, a pharmacist prepares a special mixture or formulation of a drug to meet the needs of a patient who cannot use or tolerate the product in its usual form (perhaps because of an allergy to an inactive ingredient, or an inability to swallow pills). For many years FDA left it to the states to regulate pharmaceutical compounding, but when pharmacists and hospitals started outsourcing the job to central facilities that provided compounded drugs on a larger scale, FDA took the position that these facilities were effectively making and selling new drugs without NDAs.¹⁶⁷

Congress, on the other hand, has taken a notably minimalist approach to the regulation of compounded drugs. In the FDA Modernization Act of 1997 (FDAMA),¹⁶⁸ Congress added new statutory exceptions relieving compounded drugs from various requirements for new drugs, subject to statutory limitations.¹⁶⁹ The Supreme Court held in *Thompson v. Western States Medical Center* that one of these limitations—that the pharmacy, pharmacist, or physician compounding the drug may “not advertise or promote the compounding of any particular drug, class of drug, or type of drug”—violated the First Amendment.¹⁷⁰ A decade later, the regulation of compounded drugs took on new urgency after a nationwide outbreak of fatal meningitis in patients who received injections of a compounded steroid from a compounding facility in Massachusetts.¹⁷¹ Congress responded by passing the Drug Quality and Security Act (DQSA).¹⁷² In addition to eliminating the advertising restriction that the Supreme Court had held unconstitutional, the DQSA gives compounding facilities an option of registering as “outsourcing facilities” if they are

¹⁶³21 U.S.C. § 360(k) (2012); U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., THE 510(K) PROGRAM: EVALUATING SUBSTANTIAL EQUIVALENCE IN PREMARKET NOTIFICATIONS [510(K)] GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2014).

¹⁶⁴21 U.S.C. § 360c(f)(1)(A) (2012).

¹⁶⁵Mitchell D. Feldman et al. *Who is Responsible for Evaluating the Safety and Effectiveness of Medical Devices? The Role of Independent Technology Assessment*, 23 (Suppl. 1) J. GEN. INTERNAL MED. 57, 57-63 (2008).

¹⁶⁶For an overview of the medical device industry see MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH DELIVERY SYSTEM, 207–234 (2017).

¹⁶⁷*U.S. v. Baxter Healthcare Corp.*, 901 F.2d 1401 (7th Cir. 1990).

¹⁶⁸Food and Drug Administration Modernization Act of 1997 (FDAMA) § 115, Pub. L. 105-115, 111 Stat. 2296 (1997), codified in pertinent part at 21 U.S.C. § 353a.

¹⁶⁹21 U.S.C. § 353a (2019).

¹⁷⁰*Thompson v. W. States. Med. Ctr.*, 535 U.S. 352 (2002).

¹⁷¹CTR. FOR DISEASE CONTROL & PREVENTION, MULTISTATE OUTBREAK OF FUNGAL MENINGITIS AND OTHER INFECTIONS (updated Oct. 30, 2015), <https://www.cdc.gov/hai/outbreaks/meningitis.html> [<https://perma.cc/R3PR-GQ3K>].

¹⁷²Drug Quality and Security Act, Pub. L. No. 113-54, §127 Stat. 587 (2013).

willing to comply with statutory requirements for annual registration, twice yearly reporting and submission of adverse event reports, and inspections on a risk-based schedule.¹⁷³ In effect, compounding facilities may choose between two regulatory regimes. A licensed pharmacy willing to limit its operations to compounding drugs in response to individual prescriptions can choose the FDAMA regime codified at FDCA § 503A.¹⁷⁴ A facility that wants to compound drugs on a larger scale rather than in response to individual prescriptions may choose instead the DQSA regime codified at FDCA § 503B by registering as an outsourcing facility.¹⁷⁵ Either way, the compounding facility is exempt from patient labeling and premarket approval requirements for new drugs.¹⁷⁶

Even for new drugs, Congress has encouraged FDA to shift from reliance on premarket testing towards greater use of postmarket studies in many contexts.¹⁷⁷ A 1997 amendment authorized FDA to accept data from only one “adequate and well-controlled clinical investigation” along with other “confirmatory evidence (obtained prior to or after such investigation)” as constituting “substantial evidence” of effectiveness in an NDA.¹⁷⁸

Congress encouraged the use of postapproval healthcare records as data for regulatory purposes through a legislative mandate in the Food and Drug Administration Amendments Act of 2007¹⁷⁹ (FDAAA), which FDA implements through its Sentinel Initiative.¹⁸⁰ The legislation’s objective was to improve postmarket safety monitoring of previously approved products,¹⁸¹ and the statute gave FDA significant new authorities to oversee the safety of drugs after approval.¹⁸² But

¹⁷³21 U.S.C. § 353b(b) (2019).

¹⁷⁴21 U.S.C. § 353a (2019). This option exempts them from compliance with certain requirements imposed on drug manufacturers, including current good manufacturing practice requirements.

¹⁷⁵21 U.S.C. § 353b (2019). This option exempts them from tracking requirements for pharmaceuticals enacted as part of the DQSA and codified at 21 U.S.C. § 360eee-1, but requires compliance with current good manufacturing practice requirements and prohibitions on preparing, packing, or holding drugs under insanitary conditions that other compounding pharmacists are exempt from. It also requires compliance with registration, reporting, and inspection requirements discussed in text. For a summary of the relevant law, see U.S. DEP’T. OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., GUIDANCE FOR ENTITIES CONSIDERING WHETHER TO REGISTER AS OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2015).

¹⁷⁶21 U.S.C. §§ 353a(a), 353b(a) (2019).

¹⁷⁷For a review of these changes see Laakman, *supra* note 23.

¹⁷⁸Food and Drug Administration Modernization Act of 1997 (FDAMA) § 115, Pub. L. No. 105-115, § 111 Stat. 2296 (1997), codified in pertinent part at 21 U.S.C. § 355(d) (2012).

¹⁷⁹Pub. L. No. 110-85, § 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

¹⁸⁰See The U.S. Food and Drug Administration’s Sentinel Initiative, <https://www.sentinelinitiative.org> (last visited March 17, 2019).

¹⁸¹U.S. Gov’t. Accountability Office, REPORT TO REQUESTERS: DRUG SAFETY, IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS (2006); Comm. on the Assessment of the US Drug Safety System, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC, 2–3 (2007).

¹⁸²Particularly notable are new authorities that allow FDA to require postapproval studies or new clinical trials at any time after approval of a new drug application if FDA becomes aware of new safety information, 21 U.S.C. § 355(o)(3) (2012); to require labeling changes to disclose new safety information, 21 U.S.C. § 355(p) (2012); and to require “risk evaluation and management strategy,” which might include the use of Medication Guides and patient package inserts or other communication with providers, special training or certification requirements for providers that dispense the product, and special monitoring of

Congress directed FDA to use these new authorities parsimoniously. The statute specifies that FDA shall not require postapproval clinical trials unless it determines that less onerous postapproval studies would be insufficient,¹⁸³ and shall not require postapproval studies unless it concludes that monitoring through adverse event reporting and the Sentinel System would be insufficient.¹⁸⁴ These provisions push FDA to question its traditional preference for costly clinical trials and interventional studies and to consider when it might instead rely on monitoring and observational studies using data collected in postmarket clinical settings.

Congress has provided further relief from premarket testing requirements by codifying FDA programs that accelerate approval of new drugs and biologics that address unmet medical needs for treatment of serious or life-threatening conditions.¹⁸⁵ “Accelerated approval” is available upon showing that a product has an effect on a surrogate endpoint or intermediate clinical endpoint, without having to wait for completion of longer trials that would show an effect on the ultimate clinical outcome of interest.¹⁸⁶ “Breakthrough therapy” designation, available when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies, requires closer interactions with FDA staff to improve the efficiency of clinical trial design.¹⁸⁷ “Fast track product” designation, available for a product that “demonstrates the potential to address unmet medical needs” for treatment of a serious or life-threatening disease or condition, requires FDA to take appropriate steps to accelerate development and review times.¹⁸⁸ “Priority review designation,” available for a drug that treats a serious condition and would provide a significant improvement in safety or effectiveness, requires a quick decision from FDA on an application.¹⁸⁹

As a formal matter, the standards of safety and effectiveness remain the same as for other products.¹⁹⁰ But to the extent that these programs potentially allow approval of qualifying products with less extensive premarket testing,¹⁹¹ more questions remain unanswered about their effects at the time of approval. FDA may thus require further

patients that use the product, if necessary to ensure that the benefits of the drug outweigh its risks. 21 U.S.C. § 355-1 (2012).

¹⁸³21 U.S.C. § 355(o)(3)(D)(ii) (2012).

¹⁸⁴21 U.S.C. § 355(o)(3)(D)(i) (2012).

¹⁸⁵These programs were codified in FDAMA, *supra* note 168. Their details are summarized in U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CENTER FOR DRUG EVALUATION & RESEARCH, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS – DRUGS AND BIOLOGICS (2014), available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf> [<https://perma.cc/2YD4-RBUL>] [hereinafter FDA 2014 GUIDANCE ON EXPEDITED PROGRAMS].

¹⁸⁶21 U.S.C. § 356(c) (2013).

¹⁸⁷21 U.S.C. § 356(a) (2013).

¹⁸⁸21 U.S.C. § 356(b) (2013).

¹⁸⁹FDA 2014 GUIDANCE ON EXPEDITED PROGRAMS, *supra* note 185, at 24–25.

¹⁹⁰21 U.S.C. § 356(e)(2) (2013).

¹⁹¹A controversial recent example was FDA’s fast track approval, contrary to the advice of its advisory committee, of Exondys 51 for treatment of Duchenne Muscular Dystrophy on the basis of an uncontrolled trial in only twelve patients, with a requirement for further trials. See Aaron S. Kesselheim, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 J. AM. MED. ASS’N. 2357, 2357 (2016).

postapproval studies to confirm the expected clinical benefits.¹⁹² Although FDA's expanded authorities under FDAAA include authorization to require postmarket trials, the statute dictates a preference for monitoring through the Sentinel System or through observational studies when these less onerous methods would suffice.¹⁹³

The 21st Century Cures Act of 2016¹⁹⁴ (Cures Act) is even more explicit in its directives to FDA to shift its evidentiary focus for a variety of purposes towards postapproval observational studies. The Cures Act requires FDA to develop a framework and guidance for evaluating "real world evidence" to approve new indications for previously approved drugs and to satisfy postapproval study requirements, defining "real world evidence" broadly to mean "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials."¹⁹⁵ Although the Cures Act does not authorize FDA to rely on these new data sources for initial NDA approval, it contemplates that possibility by directing FDA to "issue guidance addressing the use of complex adaptive and other novel trial design" for review and approval of new drugs and biologic products.¹⁹⁶

A number of more specific provisions embrace the use of observational studies for particular purposes. For orphan drugs, the Cures Act expands FDA's authority to award grants to defray development costs to include coverage of "prospectively planned and designed observational studies."¹⁹⁷ For regenerative medicine therapies, it provides an accelerated approval pathway and specifies that product sponsors may meet postapproval requirements through ". . . patient registries, or other sources of [real-world] evidence, such as electronic health records . . . the collection of larger confirmatory data sets . . . or . . . postapproval monitoring of all patients treated with such therapy prior to approval of the therapy."¹⁹⁸ For "breakthrough" medical devices, it provides priority review and coordination between the sponsor and FDA staff to expedite development and review, and directs FDA to "facilitate, when scientifically appropriate, expedited and efficient development and review of the device through utilization of timely postmarket data collection."¹⁹⁹

Although each of these provisions applies to a small subset of FDA's regulatory authorities, considered together, they encourage a shift from reliance on rigorous enforcement of approval standards through premarket testing requirements towards accelerated initial approval followed by ongoing data collection after products have entered clinical use. The effect is to allow clinical use of an expanding set of products to begin at an earlier stage while studies continue. Some critics have charged that

¹⁹²21 U.S.C. § 356(c)(3) (2013); FDA 2014 GUIDANCE ON EXPEDITED PROGRAMS, *supra* note 185, at 22–24.

¹⁹³21 U.S.C. § 355(o)(3)(D) (2018).

¹⁹⁴21st Century Cures Act, Pub. L. 114-255 § 3022, 103 Stat. 1033 (2016) (codified in pertinent part at 21 U.S.C. § 355g. (2016)).

¹⁹⁵*Id.* § 3022. The agency recently released a Framework for FDA's Real World Evidence Program on its website. FOOD & DRUG ADMIN., *Framework for FDA's Real World Evidence Program* (Dec. 2018), <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf> [<https://perma.cc/B2UN-3CAF>].

¹⁹⁶21st Century Cures Act, Pub. L. 114-255 § 3022, 103 Stat. 1033 (2016).

¹⁹⁷*Id.* § 3015 (codified at 21 U.S.C. § 360ee (2010)).

¹⁹⁸*Id.* § 3033 (codified at 21 U.S.C. § 356(g) (2013)).

¹⁹⁹*Id.* § 3051 (codified in pertinent part at 21 U.S.C. § 360e-3(e)(2)(C) (2016)).

shifting towards earlier approval of new technologies based on less premarket testing exposes more patients to risks that FDA might otherwise have protected them from if it continued to enforce more rigorous premarket RCT requirements.²⁰⁰ On the other hand, some risks that do not show up in RCTs may be easier to observe in larger postmarket studies, and such risks may come to light more quickly if earlier approval allows these studies to get underway sooner.²⁰¹

While leaving considerable discretion to FDA, Congress is challenging FDA to figure out how best to use the kinds of data that can be observed in postapproval clinical settings. FDA now has authority to approve many new drugs with an asterisk, while ongoing studies continue. Postmarket monitoring and observational studies are becoming more sophisticated and more rigorous as Congress has repeatedly directed FDA to consider how it can make better use of these data sources. Although some observers argue that in practice FDA remains slow and cautious in relying on its new authorities to approve applications more quickly,²⁰² the agency is surely not oblivious to the cumulative message of these legislative nudges.

The message could not have been clearer in the most recent (and aggressive) Congressional move to accelerate clinical availability of new products that do not yet meet FDCA standards for safety and effectiveness: the Right to Try Act of 2017.²⁰³ This legislation authorizes (but does not require) manufacturers to provide investigational drugs that are still in development following the completion of a Phase I trial to terminally ill patients who have exhausted approved treatment options and are not able to participate in a clinical trial.²⁰⁴ Responding to press reports that FDA would implement new regulations under the new law to balance access to medications with patient safety concerns, Senator Ron Johnson, a sponsor of the legislation, promptly sent a letter to FDA Commissioner Scott Gottlieb insisting that the new law “intends to diminish the FDA’s power over people’s lives, not increase it.”²⁰⁵

Sometimes FDA efforts to regulate products as drugs or devices have provoked legislative and judicial backlash, with Congress passing new legislation to limit FDA’s authority or courts holding its actions to be unauthorized. Notable examples include dietary supplements²⁰⁶ and tobacco products.²⁰⁷

²⁰⁰Farrah R. Raja, *Evidentiary Standards for Drug Approvals in the 21st Century Cures Act: A Continued Trend Towards Valuing Access Over Safety for Pharmaceutical Drugs*, 18 N.C.J.L. & TECH. 409, 437 (2016).

²⁰¹See Scott Gottlieb, *Opening Pandora’s Pillbox: Using Modern Information Tools to Improve Drug Safety*, 24 HEALTH AFF. 938, 939–948 (2005).

²⁰²See, e.g., Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39, 68–70 (2018) (noting that despite statutory authorization to use surrogate endpoints for accelerated approval, FDA remains conservative in using these authorities).

²⁰³See *supra* note 26.

²⁰⁴21 U.S.C. § 360bbb-0a (2019).

²⁰⁵FOOD & DRUG ADMIN., *Letter from Senator Ron Johnson to FDA Commissioner Scott Gottlieb* (May 31, 2018), <https://www.hsgac.senate.gov/imo/media/doc/2018%2005%2031%20RHJ%20to%20Gottlieb%20HHS%20re%20Right%20to%20Try.pdf> [<https://perma.cc/HUT9-JGZH>].

²⁰⁶See DSHEA, *supra* note 127, which undermined ongoing efforts at FDA to regulate dietary supplements more extensively. See John P. Swann, *The History of Efforts to Regulate Dietary Supplements in the USA*, 8 Drug Test. Analysis 271–282 at 278–79 (2016).

²⁰⁷See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (FDA regulations promulgated to reduce tobacco consumption among children and adolescents exceeded limits of its statutory

We previously considered the modified statutory regime for dietary supplements.²⁰⁸ Notable modifications include (1) placing the burden of proof on FDA to show that a dietary supplement marketed prior to 1994 “presents an unreasonable risk of illness or injury” in order to remove it from the market rather than requiring manufacturers to show safety and efficacy to gain premarket approval,²⁰⁹ and (2) a safe harbor provision that encourages manufacturers wishing to avoid regulation of their products as drugs while making permissible “health claims” to use the following prominent disclaimer:

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.²¹⁰

The Family Smoking Prevention and Tobacco Control Act of 2009 (FSPTCA)²¹¹ was enacted to give FDA new authority to regulate tobacco products after the Supreme Court rejected the agency’s effort to regulate them as drug-device combination products.²¹² The legislation prohibits FDA from banning existing tobacco products or requiring that they eliminate nicotine entirely,²¹³ but gives FDA authority to require tobacco manufacturers to disclose information about their products (including all ingredients),²¹⁴ to require annual registration and biennial inspections,²¹⁵ to restrict advertising and promotion to minors,²¹⁶ to prohibit the use of flavors other than tobacco and menthol,²¹⁷ to adopt “tobacco product standards” for the protection of public health,²¹⁸ and to assess fees to finance oversight.²¹⁹

For both dietary supplements and tobacco products, FDA has more generous authority to regulate new products that were not on the market when the legislation was enacted.²²⁰

Although some of these legislative initiatives have no direct application to medical cannabis products under current law,²²¹ they offer broader lessons for policymakers that could inform their consideration of potential regulatory alternatives. For an

authority). Congress later gave FDA new authority to regulate tobacco products in the Family Smoking Prevention and Tobacco Control Act of 2009, Pub. L. No. 111-31, 123 Stat. 1776 (2009) (codified as amended at 21 U.S.C. §§ 387 (2011)).

²⁰⁸See *supra* notes 126-135 and accompanying text.

²⁰⁹21 U.S.C. § 342(f)(1) (2011).

²¹⁰21 U.S.C. § 343(r)(6) (2011).

²¹¹See *supra* note 207.

²¹²See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000).

²¹³See 21 U.S.C. § 387g(d)(3) (2018).

²¹⁴See 21 U.S.C. § 387d(a)(2)-(3) (2018).

²¹⁵See 21 U.S.C. § 387e(b), (g) (2018).

²¹⁶See 21 U.S.C. §§ 387f(d)(1), 387f(d)(3)(A)(ii) (2018).

²¹⁷See 21 U.S.C. § 387g(a)(1)(A) (2018).

²¹⁸21 U.S.C. § 387g(a)(3)(A) (2018).

²¹⁹21 U.S.C. § 387s.(a), (c)(2)(A) (2018).

²²⁰21 U.S.C. § 350b(a), (d) (2018) (premarket notification for “new dietary ingredients”); 21 U.S.C. § 387j(a)(2)(A) (2018) (premarket approval authority for “new tobacco products”).

²²¹Some uses of medical cannabis products might qualify for FDA approval under one or more existing accelerated approval pathways; e.g., the cannabis-derived product Epidiolex benefited from both priority review and fast track designation. See *supra* notes 185-189.

expanding set of products over a period of decades, Congress has either restricted FDA's regulatory authority or directed FDA to apply that authority with a lighter touch, allowing more products to become available for clinical use with fewer premarket regulatory burdens.

These legislative initiatives sometimes reflect political constraints on the willingness of Congress to allow popular but unproven products or even products known to be harmful to be removed from the market. Sometimes they may reflect practical constraints on the ability of strict regulatory standards to serve their purposes in different contexts. When they work well, strict standards both protect patients from harm from unproven products and motivate product developers to conduct rigorous studies to test the effects of these products and to guide doctors and patients in how to use these products safely and effectively. However, strict standards are not always effective in achieving their goals. Large pharmaceutical firms that expect to sell patent-protected molecules for many years can afford to amortize large premarket R&D burdens over the life cycles of the products, while manufacturers of medical devices that are subject to continuous improvements and sellers of unpatented dietary supplements that have been on the market for many years may find similar regulatory burdens unsustainable.

A small handful of cannabis-related products have come to market under NDAs following thorough testing for safety and efficacy. But for many medical cannabis products in use today, the current regime is not doing a good job of either protecting patients from unknown risks or motivating investments in clinical trials. These products have entered into medical use without FDA approval and without the benefit of data from reliable clinical trials to guide their use. Rather than encouraging cannabis product manufacturers to test their products in premarket clinical trials, DEA registration practices currently prevent any firm that is already providing cannabis for medical use from lawfully supplying its product for use in research. Perhaps a modified regulatory approach would provide better information than the current regime.

Both FDA and DEA have made some efforts to facilitate cannabis research within the limits of current law. FDA guidance for studies of botanical drugs addresses some of the obstacles to meeting approval standards for plant products, although the small number of botanical products that have been approved to date suggests that the increased flexibilities may still be inadequate to make the regime workable.²²² DEA's proposal to increase the production quota for cannabis for use in research will presumably allow more cannabis research to proceed, although the resulting data might be more useful if researchers could use the same cannabis products that are currently available for medical use in the U.S. rather than the NCNPR/NIDA products.²²³ These modest changes are likely insufficient to make it feasible for the cannabis industry to invest in the kind of premarket clinical testing that is currently necessary to meet standards of safety and efficacy for new drugs under the FDCA and currently accepted medical use in treatment under the CSA.

A modified regulatory regime might learn more about the effects of medical use of cannabis through greater use of observational studies and patient registries to collect data on products that are already in clinical use. For most drugs, observational studies

²²²See *supra* notes 136-142 and accompanying text.

²²³See *supra* note 113 and accompanying text.

are impossible prior to FDA approval because such studies cannot proceed until clinical use begins, and most drug manufacturers are unwilling to violate the FDCA by selling unapproved products for clinical use. But clinical use of many unapproved cannabis products has already begun in states with medical cannabis laws. This quasi-legal use provides an opportunity for collecting observational data without awaiting FDA approval of an NDA.

Because such use plainly violates current federal law, further legislation would be necessary to authorize it. At a minimum, such legislation should require that sellers of unapproved products clearly inform patients that the products are experimental and that FDA has not approved their use as safe and effective for any indication. Even the minimal regulatory regime for dietary supplements under the DSHEA requires manufacturers that make “health claims” to disclose that their claims have not been evaluated by the FDA.²²⁴ Patients who use unapproved medical cannabis products with a doctor’s recommendation under color of state law may incorrectly believe that FDA has approved the use, and they are entitled to know that these products have not gone through the usual rigors of the FDA approval process.

Another modest approach to regulation of cannabis products might emulate features of the FSPTCA by requiring manufacturers to disclose information about the ingredients in their products, to register and submit to regular inspections, to restrict advertising and promotion to minors, and to restrict use of formulations designed to appeal to minors. But such measures would be insufficient to promote better data collection to study the effects of cannabis products in patients.

The FDCA requires an IND before an unapproved drug may be used for investigational purposes in humans and authorizes FDA to establish regulations governing INDs.²²⁵ This is an important source of authority that allows FDA to oversee patient safety and to guide protocols for both preclinical and clinical studies of new drugs. Although some adaptations may be necessary for medical cannabis products, FDA could use this authority to elevate standards for research in the cannabis industry and to promote collection of more data than are currently available for these products.

A modified approach for cannabis products might take advantage of the fact that cannabis products are already in clinical use in order to promote use of patient registries for collection of data on safety and effectiveness. Patients would still need to give informed consent to participation as research subjects, which would serve to remind them that FDA has not approved the products as safe and effective. A regulatory regime that makes greater use of such “real-world” data to supplement data from small clinical trials and preclinical studies might make it more feasible for cannabis firms to conduct studies and provide information about the effects of their products in patients.

In the end, FDA may still conclude that the data are insufficient to establish safety and effectiveness. There are significant limitations to the quality of data generated in registries and electronic health records that may limit what questions they can answer.²²⁶ Busy clinicians using software designed more to optimize billing than to

²²⁴See *supra* notes 133-134 and accompanying text.

²²⁵21 U.S.C. § 355(j) (2018) (granting the Secretary authority to set regulations for IND exemptions); 21 C.F.R. §§ 312.22, 312.23 (2018) (describing IND requirements).

²²⁶See Sharona Hoffman & Andy Podgurski, *Big Bad Data: Law, Public Health and Biomedical Databases*, 41 J.L. MED. & ETHICS 56, 57 (2012).

generate data may find it challenging to enter data correctly,²²⁷ and data collected in the course of treatment may lack crucial information for research purposes, such as health outcomes.²²⁸ Moreover, observational studies require cautious interpretation to avoid spurious causal inferences tainted by selection bias, confounding bias, and measurement bias.²²⁹ It may be possible to address some of these sources of bias by adapting analytic approaches from traditional randomized controlled trials to the design of trials in real-world settings, including the use of prospectively planned interventions and randomization.²³⁰

FDA has begun to address these challenges in other settings,²³¹ partly in response to mandates from Congress for medical devices²³² and supplemental indications for previously approved drugs.²³³ Observational studies are no panacea. But they are surely better than no data at all. Adaptations in the regulatory regime to encourage such studies under FDA supervision for medical cannabis products that are already in use could improve the information available to doctors and patients as well as to FDA, providing a better basis for deciding whether and how to use these products in patient care.

A possible variation would allow firms to choose their level of regulation. Firms could choose whether to submit their medical cannabis products to FDA for approval under the usual rules for new drug approval, or to sell them without that imprimatur while collecting “[real-world] evidence,” accompanied by disclaimers that FDA has not determined whether they are safe and effective. The products from firms that opt into more rigorous regulation would presumably be more costly to develop, but manufacturers of FDA-approved products might nonetheless be able to charge high enough prices to make it worthwhile, particularly if insurers were willing to pay only for FDA-approved products.²³⁴ On the other hand, if approved products face robust competition from unapproved close substitutes sold through dispensaries in the quasi-legal zone, it may be challenging to motivate firms to opt in to requirements for more costly studies.

²²⁷See ROBERT WACHTER, *THE DIGITAL DOCTOR: HOPE, HYPE, AND HARM AT THE DAWN OF MEDICINE’S COMPUTER AGE* 74, 86, 120 (2015).

²²⁸See Hoffman & Podgurski, *supra* note 226, at 56.

²²⁹See Jerry H. Gurwitz et al., *Reader’s Guide to Critical Appraisal of Cohort Studies: 1. Role and Design*, 330 *BRITISH MED. J.* 895, 895 (2005) (selection bias); Muhammad Mamdani et al., *Reader’s Guide to Critical Appraisal of Cohort Studies: 2. Assessing the Potential for Confounding*, 330 *BRITISH MED. J.* 960, 960 (2005) (confounder bias); Sharon-Lise T. Normand et al., *Reader’s Guide to Critical Appraisal of Cohort Studies: 3. Analytical Strategies to Reduce Confounding*, 330 *BRITISH MED. J.* 1021, 1022 (2005) (limitations of regression and stratification techniques).

²³⁰See Rachel E. Sherman et al., *Real-World Evidence—What Is It and What Can It Tell Us?*, 375(23) *NEW ENG. J. MED.* 2293, 2294 (2016).

²³¹See FDA 2016 REAL-WORLD EVIDENCE FOR DEVICES, *supra* note 162, at 9–11; U.S. Food & Drug Admin., *Real World Evidence* (2019), <https://www.fda.gov/scienceresearch/specialtopics/realworldevidence/default.htm> [<https://perma.cc/9475-QP49>] (discussing 21st Century Cures Act).

²³²See 21 U.S.C. § 360c(a)(3)(C), (D)(ii) (2018).

²³³See 21 U.S.C. § 355g (2018).

²³⁴*Cf.* Rebecca S. Eisenberg, *Innovation Without Patents: FDA Regulation and Insurance Coverage of DNA Diagnostics*, *MARQUETTE LAWYER*, Fall 2018, at 51–53 (explaining why laboratories already providing diagnostic genetic tests without the need for FDA approval nonetheless voluntarily sought FDA premarket clearance or approval as a strategy for obtaining insurance coverage).

Legal regulation of medical products should promote the development of better information about the effects of those products in patients. Achieving this pragmatic goal is a social problem that must respond to financial considerations as well as to scientific aspirations and public health concerns.

CONCLUSION

The current legal regime for medical use of cannabis products is unstable and has impeded the conduct of studies and generation of reliable data on the effects of cannabis products in patients. With a majority of Americans now living in states that explicitly authorize such use as a matter of state law, clinical use of cannabis products has taken root without the benefit of the rigorous trials that FDA and DEA consider necessary to change its legal status. Meanwhile, in the years since passage of the CSA, Congress has repeatedly amended the FDCA to accelerate access to medical technologies in a number of ways. Perhaps similar strategies could be adapted to design a more workable approach to studying the effects of medical cannabis products in patients, yielding more information than the current regime produces for the use of doctors and patients as well as regulators. At a minimum, federal law should require providers of medical cannabis products to comply with disclosure and disclaimer requirements that alert patients to the limits of what is currently known about the effects of these products.