

# CANNABIS DRUG DEVELOPMENT AND THE CONTROLLED SUBSTANCES ACT

GABRIELLE FELICIANI\*

## INTRODUCTION

Cannabis is a federally illegal drug in the United States, yet thirty-seven states and four territories have now enacted laws allowing the production, distribution, and consumption of cannabis for medical use. An estimated 5.5 million individuals in medical-use states<sup>1</sup> are qualified to purchase cannabis to treat and mitigate symptoms for conditions ranging from cancer to post-traumatic stress disorder to chronic pain. But, only three cannabis drugs have been approved by the Food and Drug Administration (FDA).

The sheer number of medical cannabis users demonstrates the need for a variety of FDA-approved cannabis drugs and indications for use.<sup>2</sup> The FDA drug approval process requires a demonstration of safety and effectiveness, while state medical cannabis regulations do not. There is also inconsistency in medical cannabis manufacturing processing, product quality, and availability, likely leading to less effective treatments and higher rates of adverse effects compared to FDA-approved drugs. And, although many hemp products<sup>3</sup> are purchased for their purported wellness effects, none have been approved by the FDA.<sup>4</sup>

---

\*Copyright 2023 @ Gabrielle Feliciani

J.D. Candidate, Duke University School of Law, 2023. B.A., St. John's College, 2017. Special thanks to Professor Arti Rai and the members of the *Duke Journal of Constitutional Law & Public Policy* for their guidance and assistance. For Martin, as with everything.

1. This Note refers to state-legal cannabis for medical use as “medical cannabis.”

2. Drugs are “indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.” 21 C.F.R. § 201.57(c)(2).

3. Hemp is a cannabis product containing less than 0.3% THC. Holland, *infra* note 29.

4. See, FDA, *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)*, <https://www.fda.gov/news-events/public-health-focus/fda-regulation->

The current state of federal illegality creates a problem of supply and demand—consumer demand for cannabis is high, but the number of approved drug products and indications for use remains extremely low. Federal agencies maintain that they support cannabis drug development, but current regulations add hefty requirements to the already complex and costly drug approval process. By assessing the impact of the Controlled Substances Act (CSA) on federal regulations governing cannabis drugs, this Note seeks to identify specific barriers to research and development and recommend policies to stimulate innovation. As the FDA has a responsibility to protect the public health by “ensuring the safety, efficacy, and security of human and veterinary drugs,”<sup>5</sup> it should prioritize its study of cannabis products, given that the plant and many of its chemical compounds likely have significant therapeutic potential.

Part I of this Note will provide a history of cannabis law in the United States, focusing on the federal illegality of cannabis under the CSA and the movement toward state legalization. Part II will provide an overview of the current regulatory approval process for cannabis drugs. Part III will explore the impact of the CSA on cannabis research and drug development, specifically its role in restricting the supply of cannabis for research and its impact on the current demand for cannabis drugs. Part IV will propose policy recommendations to address existing barriers created by the CSA.

## I. THE HISTORY OF CANNABIS LAW IN THE UNITED STATES

It is currently illegal to produce, distribute, possess, or consume synthetic cannabis or any part of the cannabis plant under federal law. But, low-THC cannabis (hemp) is no longer considered an illicit substance, and most states<sup>6</sup> currently allow cannabis to be marketed and consumed for medical purposes. This Part provides additional

---

cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#approved (Jan. 22, 2021) (“Aside from Epidiolex . . . [t]here are no other FDA-approved drug products that contain CBD.”).

5. FDA, *What We Do*, <https://www.fda.gov/about-fda/what-we-do> (Mar. 28, 2018).

6. Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, Virginia, Washington, and West Virginia currently allow cannabis use for medical purposes. *State Medical Cannabis Laws*, NAT’L CONF. OF STATE LEGS. (Feb. 3, 2022), <https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>.

information about these legal systems and explains how they square with the current scientific understanding of cannabis.

### A. *Cannabis Federalism*

Criminalization of cannabis started in the early 1900s when states began to outlaw its use following the Mexican Revolution of 1910.<sup>7</sup> Congress then federally criminalized the substance with the passage of the Marijuana Tax Act in 1937 and passed mandatory sentencing laws in the 1950s.<sup>8</sup> Despite some movement toward repealing these sentencing laws in the intervening decades,<sup>9</sup> the passage of the CSA<sup>10</sup> in 1970 solidified cannabis's illegality and ushered in the modern era of cannabis policy in the United States.

The CSA places controlled substances into one of five schedules<sup>11</sup> based on their “medical use, potential for abuse, and safety or dependence liability.”<sup>12</sup> Cannabis is a Schedule I substance,<sup>13</sup> subject to the most stringent controls and deemed to have “a high potential for abuse,” “no currently accepted medical use in treatment,” and “a lack of accepted safety for use . . . under medical supervision.”<sup>14</sup> Therefore, the CSA makes it illegal to “produce, dispense, or distribute” these substances except for use in federally approved research studies,<sup>15</sup> and the Drug Enforcement Administration (DEA) is authorized to enforce CSA provisions through a variety of civil and criminal penalties.<sup>16</sup>

The FDA is primarily responsible for enforcing the Food, Drug, and Cosmetic Act (FDCA), which prohibits “introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is adulterated or misbranded.”<sup>17</sup> Prescription drugs that are also controlled substances (controlled medications) are subject to DEA and

---

7. *Marijuana Timeline*, FRONTLINE, <https://www.pbs.org/wgbh/pages/frontline/shows/dope/etc/cron.html> (last visited Apr. 4, 2022).

8. *Id.*

9. *Id.*

10. The Controlled Substances Act (CSA) of 1970, Pub. L. No. 91-513, 84 Stat. 1242.

11. See Harrison Jacobs, *The DEA Treats Heroin and Marijuana as Equally Dangerous Drugs*, BUS. INSIDER (May 22, 2016, 5:54 PM), <https://www.businessinsider.com/us-drug-scheduling-system-heroin-marijuana-2016-5>, for an overview of the CSA's scheduling criteria.

12. DEA, *The Controlled Substances Act*, <https://www.dea.gov/drug-information/drug-policy> (last visited Apr. 4, 2022).

13. 21 U.S.C. § 812(c)(10), (17).

14. See 21 U.S.C. § 812 (defining and listing Schedule I substances).

15. JOANNA R. LAMPE, CONG. RSCH. SERV., R45948, THE CONTROLLED SUBSTANCES ACT (CSA): A LEGAL OVERVIEW FOR THE 117TH CONGRESS 31 (2021).

16. See generally 21 U.S.C. §§ 841–65.

17. 21 U.S.C. § 331(a).

FDA oversight and must therefore comply with CSA and FDCA requirements.<sup>18</sup>

In the thirty-seven states and four territories that allow individuals with qualifying medical conditions to purchase cannabis,<sup>19</sup> licensed cultivators and manufacturers can grow and process cannabis,<sup>20</sup> and health care providers can recommend medical cannabis to patients with qualifying conditions.<sup>21</sup> The federal government has notably chosen not to interfere with these state-run programs.<sup>22</sup> Under this regulatory scheme, an estimated 5.5 million people<sup>23</sup> use medical cannabis to treat qualifying conditions such as cancer, epilepsy, HIV/AIDS, irritable bowel disease, post-traumatic stress disorder, multiple sclerosis, chronic pain, and various others.<sup>24</sup>

### B. Terminology and Legal Distinctions

The legal and scientific literature varies in its treatment of cannabis. *Cannabis sativa* is a plant containing over five hundred chemical substances.<sup>25</sup> The CSA defines “marihuana” as “all parts of the plant

18. LAMPE, *supra* note 15 at 4.

19. NAT'L CONF. OF STATE LEGS., *supra* note 6.

20. See generally Barry Weisz & Michael Rosenblum, *Cannabis State-By-State Regulations*, THOMPSON COBURN LLP, <https://www.thompsoncoburn.com/docs/default-source/blog-documents/ranking-of-state-cannabis-regulations.pdf> (Aug. 2021).

21. Joseph Gregorio, *Physicians, Medical Marijuana, and the Law*, 16 AMA J. OF ETHICS 732, 733 (2014). Although the CSA forbids physicians from prescribing medical cannabis, *Conant v. Walters*, 309 F.3d 629, 633 (9th Cir. 2002), courts have found that they may recommend its use, see, e.g., *id.* at 635–36 (holding that doctors cannot anticipate that their patients will use their cannabis recommendations to violate federal law, therefore their recommendations do not constitute aiding and abetting or conspiracy). The recently enacted Medical Marijuana and Cannabidiol Research Expansion Act also states that “[i]t shall not be a violation of the Controlled Substances Act (21 U.S.C. 801 et seq.) for a State-licensed physician to discuss— (1) the currently known potential harms and benefits of marijuana derivatives, including cannabidiol, as a treatment with the legal guardian of the patient of the physician if the patient is a child; or (2) the currently known potential harms and benefits of marijuana and marijuana derivatives, including cannabidiol, as a treatment with the patient or the legal guardian of the patient of the physician if the patient is a legal adult.” Pub. L. No. 117-215, § 301, 136 Stat. 2265 (2022) (codified as amended in 21 U.S.C. § 801).

22. See Bradley E. Marakano, *Enabling State Deregulation of Marijuana Through Executive Branch Nonenforcement*, 90 NYU L. REV. 289, 294–95 (2015) (explaining how DOJ Ogden and Cole memos outline the government’s tacit acceptance of state cannabis operations).

23. *Medical Marijuana Patient Numbers*, MARIJUANA POL’Y PROJECT, <https://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-patient-numbers/> (May 27, 2021).

24. Kevin F. Boehnke et al., *Qualifying Conditions of Medical Cannabis License Holders in the United States*, 38 HEALTH AFFS. 295, 300 (2009).

25. NIH, *Cannabis (Marijuana) and Cannabinoids: What You Need to Know*, <https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know> (Nov. 2019).

*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.”<sup>26</sup>

Delta-9 tetrahydrocannabinol (THC) is the main psychoactive component of cannabis and is primarily found in glandular trichomes of female cannabis flowers, although low amounts are found in other cannabis plant material.<sup>27</sup> THC binds with two endogenous cannabinoid receptors, CB1 and CB2.<sup>28</sup> Cannabidiol (CBD) is another component of cannabis that is structurally similar to THC but does not produce psychoactive effects.<sup>29</sup> CBD does not appear to act directly at cannabinoid receptors but may interact with the endocannabinoid system indirectly and modulate non-endocannabinoid signaling systems.<sup>30</sup>

“Marijuana” and “[t]etrahydrocannabinols” are the specific substances included under Schedule I of the CSA.<sup>31</sup> Since first placing them in Schedule I, Congress passed the Agriculture Improvement Act of 2018 (Farm Bill),<sup>32</sup> which removed “hemp” from the CSA’s definition of tetrahydrocannabinol.<sup>33</sup> The Farm Bill defined hemp as cannabis plant material “with a delta-9 tetrahydrocannabinol concentration of not more than 0.3% on a dry weight basis.”<sup>34</sup> In doing so, Congress created a legal distinction between THC and CBD. Although cannabis containing over 0.3% THC is a Schedule I substance, cannabis with 0.3% THC or less, including cannabis containing other chemical

---

26. 21 U.S.C. § 802(16)(A).

27. Samuel D. Banister et al., *Dark Classics in Chemical Neuroscience: Δ9-Tetrahydrocannabinol* ACS Chemical Neuroscience, 10 ACS CHEM. NEUROSCIENCE 2160, 2161 (2019).

28. *Id.* at 2163.

29. Kimberly Holland, *CBD vs. THC: What’s the Difference?*, HEALTHLINE, <https://www.healthline.com/health/cbd-vs-thc> (July 20, 2020).

30. WORLD HEALTH ORGANIZATION [WHO] SECRETARIAT, *CANNABIDIOL (CBD) Critical Review Report*, 12–13 (2018). The endocannabinoid system is cell-signaling system that involves endocannabinoids, receptors, and enzymes. Crystal Raypole, *A Simple Guide to the Endocannabinoid System*, HEALTHLINE (May 17, 2021), <https://www.healthline.com/health/endocannabinoid-system>. Endocannabinoids occur naturally in the body and bind to receptors CB1 and CB2 found in the central and peripheral nervous system respectively. *Id.*

31. 21 U.S.C. § 812(c)(10), (17).

32. Agriculture Improvement Act of 2018 (Farm Bill), Pub. L. No. 115-334, 133 Stat. 4490 (codified as amended in scattered sections of 7 U.S.C.). The Farm Bill gave U.S. Department of Agriculture (USDA) primary authority over hemp. *Id.*

33. 21 U.S.C. § 812(c)(17).

34. 7 U.S.C. § 1639(o)(1).

compounds such as CBD,<sup>35</sup> has been descheduled. Still, hemp remains subject to USDA and FDA regulation.<sup>36</sup>

Synthetic compounds “chemically produced to mimic tetrahydrocannabinol (THC)” are also strictly regulated.<sup>37</sup> Synthetic cannabis was “first produced for research purposes to study the effects of cannabinoids on brain functioning and their efficacy in treating pain.”<sup>38</sup> Some synthetic compounds, like dronabinol<sup>39</sup> are naturally occurring in cannabis plants, whereas others, like nabilone,<sup>40</sup> can only be created in a laboratory.<sup>41</sup> Congress enacted the Synthetic Drug Abuse Prevention Act of 2012 following reports of increased illicit use of synthetic cannabis, which placed “synthetic cannabinoids” into Schedule I of the CSA.<sup>42</sup> As a result, the DEA now regulates “synthetic equivalents of the substances contained in the cannabis plant . . . with similar chemical structure and pharmacological activity” as Schedule I substances.<sup>43</sup>

This Note will generally refer to products derived from or synthetically equivalent to the *cannabis sativa* plant as “cannabis” and distinguish between THC and CBD where helpful and appropriate. It will refer to synthetic cannabinoids as “synthetic cannabis” and plant-derived compounds as “cannabis-derived.” And, it will refer to

35. Another cannabis compound, commonly known as Delta-8, has psychoactive effects but is technically legal, as it contains less than 0.3% delta-9 THC. Douglas R. Sargent & David Standa, *FDA and CDC Issue Warnings Regarding Delta-8 THC, Which Remains in Legal Grey Area*, GREENSPOONMARDER LLP (Sept. 15, 2021), <https://www.gmlaw.com/news/fda-and-cdc-issue-warnings-regarding-delta-8-thc-which-remains-in-legal-grey-area/>. But, the DEA has moved to consider all “[a]ll synthetically derived tetrahydrocannabinols [as] schedule I controlled substances” in a proposed rule currently being challenged in court. *Id.* (quoting Implementation of the Agriculture Improvement Act of 2018, 85 Fed. Reg. 51639, 51641 (Aug. 21, 2020) (to be codified at 21 C.F.R. pts. 1308, 1312)).

36. Stephen M. Hahn & Amy Abernethy, *Better Data for a Better Understanding of the Use and Safety Profile of Cannabidiol (CBD) Products*, FDA, <https://www.fda.gov/news-events/fda-voices/better-data-better-understanding-use-and-safety-profile-cannabidiol-cbd-products> (Jan. 8, 2021).

37. LISA N. SACCO & KRISTIN FINKLEA, CONG. RSCH. SERV., R42066, SYNTHETIC DRUGS: OVERVIEW AND ISSUES FOR CONGRESS 6 (2016).

38. *Id.*

39. *See infra* notes 113–120 and accompanying text for in depth discussion of dronabinol.

40. *See infra* notes 121–125 and accompanying text for in depth discussion of nabilone.

41. FDA, *FDA and Cannabis: Research and Drug Approval Process*, <https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process> (Oct. 1, 2020).

42. SACCO & FINKLEA, *supra* note 37.

43. Interpretation of Listing of “Tetrahydrocannabinols” in Schedule I, 66 Fed. Reg. 51530, 51531 (Oct. 9, 2001). “[A]ny material, compound, mixture, or preparation that falls within the definition hemp” remains exempted from the CSA, 21 C.F.R. § 1308.11(31)(i), but no specific language in the statute or federal regulations addresses synthetic hemp.

prescription drugs containing controlled substances as “controlled medications.”

## II. THE CURRENT APPROVAL PROCESS FOR CANNABIS DRUGS

The FDA has established a series of regulatory processes for approving drugs. This Part will provide an overview of this process as it relates to cannabis drugs, beginning with how the FDA classifies cannabis drugs and then turning to the cannabis drug development process and the requirements for investigational new drugs (INDs) and new drug applications (NDAs). Finally, it will discuss all three FDA-approved cannabis drugs and their various exclusivities and indications.

### A. *Cannabis Drug Classifications*

To determine the proper approval process for a product regulated by the FDA, the agency must first classify it as a drug, biologic, medical device, or combination product.<sup>44</sup> A product class determination is “based on statutory definitions, as set forth in sections 201(g) and 201(h) of the [FDCA], respectively.”<sup>45</sup> The FDA then applies the available scientific evidence on a product’s proposed uses and indications to the statutory definitions to make its product determination.<sup>46</sup> This Section focuses on the FDA’s classification process and, for reasons discussed below, determines that the FDA will almost certainly consider all cannabis drugs as small molecule drugs and not as botanical drugs.

#### 1. Botanical Drugs

The FDA regulates botanicals<sup>47</sup> and defines a botanical drug product as “plant materials, algae, macroscopic fungi, and combinations thereof . . . intended for use in diagnosing, curing, mitigating, or treating disease.”<sup>48</sup> The FDA has published guidance on botanical drug development, identifying unique challenges associated with botanical research that affect the information required in a botanical drug’s IND

---

44. FDA, CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES: GUIDANCE FOR INDUSTRY AND FDA STAFF 2 (2017).

45. *Id.* at 4.

46. *Id.*

47. Carmen Tamayo & Freddie Ann Hoffman, *Botanical Regulation: Comparison of the United States and Canada*, 6 PHARM. REGUL. AFFS. 1, 1 (2017).

48. FDA, BOTANICAL DRUG DEVELOPMENT GUIDANCE FOR INDUSTRY 2–3 (2016) [hereinafter BOTANICAL GUIDANCE].

application.<sup>49</sup> For one, botanical drugs must “fully characterize, define, and demonstrate consistency in chemical composition,”<sup>50</sup> but heterogeneous mixtures in plant materials are not well defined, their active constituents are not always identified, and their biological activities are not well characterized.<sup>51</sup> For this reason, the FDA has approved only two botanical drug applications despite receiving more than five hundred botanical drug INDs since 1999.<sup>52</sup> A cannabis-derived botanical drug would be formulated using extracts from the actual cannabis plant, and its heterogeneous mixture would likely contain “phytocannabinoids THC and/or CBD, and possibly additional cannabis constituents such as other phytocannabinoids, terpenoids, and flavonoids.”<sup>53</sup>

## 2. Small Molecule Drugs

Small molecule drugs are “[synthetic] compounds with low molecular weight that are capable of modulating biochemical processes to diagnose, treat, or prevent diseases.”<sup>54</sup> Small molecule drugs make up about 90 percent of the pharmaceutical drug market.<sup>55</sup> Due to their prevalence, the standards for researching and developing small molecule drugs are clear, and there are “established methods for manufacturing, testing, and quality control from start to finish.”<sup>56</sup> Small molecule drugs—as opposed to the “heterogeneous mixture”<sup>57</sup> in botanical drug products—are more attractive to drug developers because of their ease of testing and manufacturing, predictability, and shelf stability.<sup>58</sup>

49. *Id.* at 5.

50. Marcel O. Bonn-Miller et al., *Cannabis and Cannabinoid Drug Development: Evaluating Botanical Versus Single Molecule Approaches*, 30 INT’L REV. OF PSYCHIATRY 277, 282 (2018).

51. BOTANICAL GUIDANCE, *supra* note 48, at 5. THC is the most widely studied and understood cannabis molecule, but scientists continue to discover and research other constituents present in cannabis plants. Bonn-Miller et al., *supra* note 50, at 280.

52. Kyungseop Ahn, *The Worldwide Trend of Using Botanical Drugs and Strategies for Developing Global Drugs*, 50 BMB Reports 111, 112 fig.1 (2017).

53. Daniel L. Flint & Deborah M. Shelton, *Cannabis-Derived Botanical Drugs: A Viable Regulatory Pathway for Marketing Medical Edibles?*, 74 FOOD & DRUG L. J. 212, 225 (2019).

54. Huy X. Ngo & Sylvie Garneau-Tsodikova, *What are the Drugs of the Future?*, 9 CHEMCEHEMCOMM 757, 757 (2018).

55. Yuval Cohen, *Small Molecules: The Silent Majority of Pharmaceutical Pipelines*, XCONOMY (Nov. 23, 2015), <https://xconomy.com/boston/2015/11/23/small-molecules-the-silent-majority-of-pharmaceutical-pipelines/>.

56. Bonn-Miller et al., *supra* note 50, at 283.

57. Flint & Shelton, *supra* note 53, at 225.

58. See Ngo & Garneau-Tsodikova, *supra* note 54, at 757–58 (finding that low weight and simple chemical structures of small molecule drugs contribute to these characteristics).



### 3. Cannabis Classification

The FDA indicated it would consider cannabis-derived drugs to be botanical drugs in its cannabis drug development guidance.<sup>59</sup> But, it has so far considered all synthetic and cannabis-derived drugs as small molecule drugs.<sup>60</sup> This is most likely because the FDA’s definition of botanical drugs excludes “highly purified drug substances” and “materials derived from genetically modified botanical species.”<sup>61</sup> A cannabis-derived drug would fall into this exclusion for two reasons. First, “medical or therapeutic applications require [cannabis] products to be ultra-pure (beyond 99 percent purity).”<sup>62</sup> This purification process would remove a resulting drug from the botanical designation. Second, the number of genetically modified cannabis plants is growing, with biotech and drug companies snapping up patents for novel isolated genes and genetically modified plant cells taken from naturally occurring cannabis strains.<sup>63</sup> And, as synthetic compounds contain no

---

59. *FDA & Cannabis: Research and Drug Approval Process*, *supra* note 41 (“FDA supports those in the medical research community who intend to study cannabis by . . . updat[ing] its Guidance for Industry: Botanical Drug Development, which provides sponsors with guidance on submitting investigational new drug (IND) applications for botanical drug products.”).

60. *Nabilone*, DRUGBANK ONLINE, <https://go.drugbank.com/drugs/DB00486> (Apr. 1, 2022, 8:23 PM); *Dronabinol*, DRUGBANK ONLINE <https://go.drugbank.com/drugs/DB00470> (Apr. 1, 2022, 8:23 PM). “FDA excludes highly purified substances from its description of botanical drugs. For this reason, FDA recently declined to review [Epidiolex] as a botanical NDA because it was formulated with a highly purified preparation of CBD. This was the case even though the preparation of CBD was a plant-derived extract from cannabis. In contrast, a less-purified, cannabis-derived extract more closely resembling the natural spectrum of constituents present in the flowering tops of cannabis (e.g., phytocannabinoids and terpenoids) should generally be eligible for development as a botanical drug.” Flint & Shelton, *supra* note 53, at 225.

61. Sau (Larry) Lee, Acting Assoc. Dir. for Science, FDA Office of Pharm. Quality, Address at the FDA/PQRI Conference on Advancing Product Quality: Botanical Drug Development and Quality Standards 4 (Oct. 6, 2015).

62. Mehrab Valizadehderakhshan et al., *Extraction of Cannabinoids from Cannabis sativa L. (Hemp)—Review*, 11 AGRICULTURE 384, 388 (2021).

63. See Chris Arsenault, *Investors rush to patent genetically modified cannabis molecules*, CBC NEWS (Oct. 16, 2018), <https://www.cbc.ca/news/business/cannabis-genetic-biotech-patents-gmo-1.4854746> (“[S]cientists are working on the latest frontier in the cannabis business: genetically engineering the active ingredients in marijuana and then patenting them.”); *22nd Century Group Achieves Breakthrough Hemp/Cannabis GMO Technology; Granted New Patent for Controlling Genes Responsible for Production of CBD, THC, and Other Valuable Cannabinoids*, GLOBALNEWswire (Dec. 17, 2020, 10:10 AM), <https://www.globenewswire.com/news-release/2020/12/17/2147171/0/en/22nd-Century-Group-Achieves-Breakthrough-Hemp-Cannabis-GMO-Technology-Granted-New-Patent-for-Controlling-Genes-Responsible-for-Production-of-CBD-THC-and-Other-Valuable-Cannabinoids.html> (explaining that cannabis GMOs “can potentially increase the yield of plants, stabilize the level of cannabinoids that are produced, and create custom cannabinoid profiles optimized for specific therapeutic uses”). But, some companies remain focused on “isolating particular cannabinoids from the cannabis plant in order to make new medicines” rather than on genetic modifications. Arsenault, *supra* note 63.

plant material, drugs containing synthetic cannabis would also surely be considered small molecule drugs by the FDA. For these reasons, this discussion of the cannabis drug approval process will focus on small molecule drug development.

### B. *The Drug Development Process*

The small molecule drug development path begins with basic research and preclinical development before the drug sponsor submits its IND application for clinical trial approval.<sup>64</sup> The drug sponsor then proceeds with Phase I, II, and III clinical trials and submits their NDA with its clinical trial results and other information.<sup>65</sup> If approved by the FDA, the drug may be marketed, and post-marketing reporting and studies may occur.<sup>66</sup>

#### 1. IND Process for Cannabis-Derived Drugs

Although cannabis-derived drugs will be considered small molecule drugs, researchers must initially obtain cannabis plant material or extracts from DEA-approved suppliers to use in clinical studies.<sup>67</sup> As the law currently stands,<sup>68</sup> even products composed solely of a purified cannabinoid will ultimately be subject to both botanical drug product and small molecule drug product requirements.<sup>69</sup>

Drugs that are not “generally recognized among experts” as safe and effective for a specified therapeutic use must obtain an IND from

64. See AGATA DABROWSKA & SUSAN THAUL, CONG. RSCH. SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 4 fig.1. (2018) for a general overview of the drug development path.

65. *Id.* at 5.

66. *Id.* at 7–8.

67. See Alice Mead, *Legal and Regulatory Issues Governing Cannabis and Cannabis-Derived Products in the United States*, 10 FRONTIERS IN PLANT SCIENCE, 697, 704–05 (2019) (“[C]annabinoid product[s] must undergo a full range of preclinical and clinical safety and efficacy testing, including drug/drug and food/drug interaction studies. In addition, because a cannabinoid product is derived from the cannabis plant and is therefore generally considered to be active in the central nervous system, the product must go through a battery of tests to determine the extent (or not) of its abuse potential: receptor binding and preclinical studies, as well as a special human abuse liability study.”).

68. The described IND process for cannabis-derived drugs will likely change following implementation of the Medical Marijuana and Cannabidiol Research Expansion Act. Pub. L. No. 117-215, 136 Stat. 2257 (2022) (codified as amended in scattered sections of 21 U.S.C.). See *infra* notes 211–16 and accompanying text.

69. See Mead, *supra* note 67, at 705 (“FDA has issued a guidance to assist sponsors in developing botanically complex prescription medications . . . by the time [a botanically complex prescription] product reaches Phase 3, the requirements are essentially the same as for any product composed of a single synthetic molecule. If the product is composed solely of a purified cannabinoid, it is subject to all such requirements.”).

the FDA before developers can conduct Phase I, II, or III clinical trials.<sup>70</sup> The FDA has recommended that cannabis-derived drug sponsors seek IND approval.<sup>71</sup> IND submissions for cannabis-derived drugs containing over 0.3% THC (THC-derived drugs) should: 1) obtain a pre-IND number and request a pre-IND meeting with the FDA Center for Drug Evaluation and Research (CDER); 2) obtain information from a DEA-registered source of cannabis for information on chemistry, manufacturing, and controls (CMC) and botanical raw material (BRM); 3) contact the DEA with Schedule I drug research plans and discuss a potential “investigator and study site Schedule I license;”<sup>72</sup> 4) compile CMC data characterizing the study drug and ensuring that it is safe for human use; and 5) submit a copy of the IND, clinical protocol, and Letter of Authorization.<sup>73</sup> After IND submission, the FDA reviews the submitted IND for thirty days to ensure that the study will not place subjects at an unreasonable risk.<sup>74</sup> The sponsor cannot initiate clinical trials during this period unless notified, and, if the FDA authorizes the IND, the sponsor must then obtain protocol registration<sup>75</sup> from the DEA and obtain the cannabis to begin the study.<sup>76</sup>

Cannabis-derived drugs containing 0.3% THC or less (CBD-derived drugs) have an easier path to IND submission. The FDA recommends that sponsors: 1) obtain a pre-IND number and request a pre-IND meeting with CDER; 2) provide the proposed drug’s CMC and BRM for FDA review, including hemp cultivars; 3) compile CMC data characterizing the study drug and ensuring it is safe for use in humans; and 4) submit a copy of the IND, clinical protocol, and Letter of Authorization.<sup>77</sup> As in the THC-derived IND process, the FDA must review the submitted IND for thirty days before the study can commence.<sup>78</sup>

---

70. FDA, CANNABIS AND CANNABIS-DERIVED COMPOUNDS: QUALITY CONSIDERATIONS FOR CLINICAL RESEARCH GUIDANCE FOR INDUSTRY 2 (2020) [hereinafter CANNABIS AND CANNABIS-DERIVED COMPOUNDS].

71. *FDA and Cannabis: Research and Drug Approval Process*, *supra* note 41.

72. *See* 21 C.F.R. § 1301.32 (2022) (outlining process for Schedule I license determinations).

73. *See FDA and Cannabis: Research and Drug Approval Process*, *supra* note 41 (outlining process for THC-derived drug approval).

74. *Id.*

75. *See* 21 C.F.R. § 1301.18 (2022) (describing elements of DEA protocol registration).

76. *FDA and Cannabis: Research and Drug Approval Process*, *supra* note 41.

77. *See id.* (outlining process for CBD-derived drug approval).

78. *Id.*

## 2. IND Process for Synthetic Cannabis Drugs

The FDA largely regulates synthetic cannabis drugs like it does other small molecule drugs.<sup>79</sup> IND Applications for small molecule drugs must include: the clinical study design; animal test data; lead investigator qualifications; written approval of an Institutional Review Board that has determined that “study participants will be made aware of the drug’s investigative status and that any risk of harm will be necessary, explained, and minimized;” and an “Indication for Use” section that includes a description of the drug’s effect, the clinical condition it intends to treat, and its target population.<sup>80</sup> But, synthetic cannabis drug sponsors must also obtain a Schedule I researcher and manufacturer license from the DEA to synthesize them.<sup>81</sup>

## 3. NDA Elements

The NDA process does not explicitly differentiate between controlled and non-controlled substances but instead highlights the safety of the proposed drug.<sup>82</sup> The drug sponsor must submit its clinical trial results showing safety and efficacy.<sup>83</sup> Phase I clinical studies test for the drug’s safety among a small number of human volunteers.<sup>84</sup> Phase II and III clinical studies must demonstrate safety, along with “efficacy and effectiveness in larger groups of individuals with the particular characteristic, condition, or disease.”<sup>85</sup> Clinical trial rate success for small molecule drugs across all industries sits at about 13 percent,<sup>86</sup> and success rates are lowest between Phase II and Phase III.<sup>87</sup>

79. CANNABIS AND CANNABIS-DERIVED COMPOUNDS, *supra* note 70, at 1.

80. DABROWSKA & THAUL, *supra* note 64, at 4–5.

81. See Sandra D. Comer et al., *Potential Unintended Consequences of Class-Wide Drug Scheduling Based on Chemical Structure: A Cautionary Tale for Fentanyl-Related Compounds*, 221 DRUG & ALCOHOL DEPENDENCE 108530, 108536 (2021) (remarking that fentanyl’s Schedule I status requires Schedule I Manufacturer and Distributor Licenses, which “may affect the development of small molecule analgesics as well as vaccines or antibodies targeting fentanyl and its analogs”).

82. BOTANICAL GUIDANCE, *supra* note 48, at 23.

83. DABROWSKA & THAUL, *supra* note 64, at 6.

84. *Id.* at 5.

85. *Id.*

86. See RYAN KIMMITT & MARCELA VIEIRA, RESEARCH SYNTHESIS: TIME AND SUCCESS RATE OF PHARMACEUTICAL R&D, KNOWLEDGE PORTAL ON INNOVATION & ACCESS TO MEDS. 10 (July 2020) (finding a 13 percent small molecule drug success rate in some research studies and finding rates fluctuating from 5 percent to 15 percent in others).

87. Chi Heem Wong et al., *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 BIostatistics 273, 279 tbl.2 (2019); *Large vs. Small Molecule Success Rates*, APPLIED CLINICAL TRIALS (Sept. 17, 2016), <https://www.appliedclinicaltrials.com/view/large-vs-small-molecule-success-rates>.

Trials become increasingly more expensive throughout the drug development progress.<sup>88</sup> Phase III clinical studies cost an average of \$20 million,<sup>89</sup> and drug sponsors must provide at least two adequate and well-controlled Phase III studies showing “convincing evidence of effectiveness.”<sup>90</sup>

In addition to clinical trial data, NDAs must include: the drug’s proposed labeling; patent information; a showing that the proposed manufacturing process and facilities are adequate to preserve the drug’s identity, strength, quality, and purity; a product description; the drug’s indication; and risk evaluation and mitigation strategy.<sup>91</sup> If approved, the FDA requires that manufacturers report all serious and unexpected adverse reactions and may also require post-marketing studies.<sup>92</sup>

#### 4. Expedited Processes

Some cannabis drugs can take advantage of FDA designations that facilitate the drug development process and expedite approval.<sup>93</sup> Fast Track designation is available for drugs that “treat serious conditions

---

88. See AYLIN SERTKAYA ET AL., EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS TO DEVELOPMENT, E. RSCH. GRP. 3–4 fig.4 (2014) (estimating Phase I trials at \$4 million, Phase II trials at \$13 million, and Phase III trials at \$20 million).

89. *Id.*

90. DABROWSKA & THAUL, *supra* note 64, at 6.

91. *Id.* at 5–6; BOTANICAL GUIDANCE, *supra* note 48, at 24.

92. DABROWSKA & THAUL, *supra* note 64, at 16–17.

93. *FDA and Cannabis: Research and Drug Approval Process*, *supra* note 41. Epidiolex received Priority Review designation and Fast Track designation. *FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy*, *infra* note 100; *GW Pharmaceuticals Announces Epidiolex® Receives Fast Track Designation from FDA for the Treatment of Dravet Syndrome*, GW PHARMS. (June 6, 2014) [hereinafter *Epidiolex Announcement*], <https://web.archive.org/web/20200807212944/https://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-announces-epidiolexr-receives-fast-track>. Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review were implemented after Marinol and Cesamet were approved in 1985. See *infra* notes 113, 121 and accompanying text; see also FDA, *Food and Drug Administration Modernization Act (FDAMA) of 1997*, <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-modernization-act-fdama-1997> (Mar. 29, 2018) (authorizing Fast Track designation on November 21, 1997); FDA, *Fact Sheet: Breakthrough Therapies*, <https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies> (Mar. 28, 2018) (authorizing Breakthrough Therapy designation on July 9, 2012); New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942, 58942 (Dec. 11, 1992) (to be codified at 21 C.F.R. pts. 314, 501) (implementing Accelerated Approval on December 11, 1992); Prescription Drug User Fee Act, Pub. L. No. 102-571, 101 Stat. 449 (codified as amended at 21 U.S.C. §§ 301, 379g) (amending the FDCA to on October 5, 1992, to authorize Priority Review).

and fill unmet needs,”<sup>94</sup> and Breakthrough Therapy designations exist for drugs that “may demonstrate substantial improvement over available therapy on a clinically significant endpoint.”<sup>95</sup> These designations have the same safety and efficacy standards as the normal development process but allow the sponsor more meetings with the FDA.<sup>96</sup> Accelerated Approval also applies to drugs that treat serious conditions fulfilling unmet needs, and it allows the FDA to approve the drugs based on surrogate endpoints or intermediate clinical outcomes.<sup>97</sup> Finally, Priority Review shortens the FDA’s review timeline for NDAs that “would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.”<sup>98</sup>

### C. FDA-Approved Cannabis Drugs

The FDA has approved one CBD-derived drug and two synthetic THC drugs to date. The FDA granted approval to GW Pharmaceuticals (GW)<sup>99</sup> for Epidiolex on June 25, 2018.<sup>100</sup> Epidiolex is an oral solution derived from CBD indicated for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.<sup>101</sup> GW received Fast Track designation for Epidiolex, as Lennox-Gastaut and Dravet syndromes are rare conditions with no available, comparable treatments.<sup>102</sup> GW submitted three randomized, double-blind, and placebo-controlled clinical trials in its NDA to demonstrate

---

94. FDA, *Fast Track*, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track> (Jan. 4, 2018).

95. FDA, *Breakthrough Therapy*, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy> (Jan. 4, 2018). Clinically significant endpoints “measure[] an effect on irreversible morbidity or mortality or on symptoms that represent serious consequences of the disease.” *Id.*

96. DABROWSKA & THAUL, *supra* note 64, at 9

97. *Breakthrough Therapy*, *supra* note 95; *see also* DABROWSKA & THAUL, *supra* note 64, at 9 n.41 (“A surrogate endpoint ‘is a marker . . . that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.’ An *intermediate clinical endpoint* . . . is a “measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug.””).

98. FDA, *Priority Review*, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review> (last updated Jan. 4, 2018); DABROWSKA & THAUL, *supra* note 64, at 9.

99. GW was recently acquired by Jazz Pharmaceuticals. Volkman, *infra* note 195.

100. FDA, *FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy*, (June 25, 2018), <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms>.

101. *Id.*; *Epidiolex Announcement*, *supra* note 93.

102. *Epidiolex Announcement*, *supra* note 93.

effectiveness.<sup>103</sup> Epidiolex’s approval caused the DEA to reschedule<sup>104</sup> it and any future generic versions to Schedule V.<sup>105</sup> The DEA later descheduled<sup>106</sup> Epidiolex but did not make a general scheduling determination about future approved CBD-derived drugs.<sup>107</sup>

Post-approval research studies of Epidiolex have suggested that it has potential for use in treating pain, anxiety, autism, schizophrenia, migraines, infantile spasms, and multiple sclerosis.<sup>108</sup> And, “[o]ff-label use of CBD is emerging with compassionate use, open-label prospective studies and case series describing its use for genetic epilepsy syndromes . . . and in febrile infection-related epilepsy syndrome (FIRES) for both the acute and chronic management of seizures.”<sup>109</sup> But, the FDA has approved only one subsequent indication for Epidiolex for the treatment of seizures associated with tuberous sclerosis complex.<sup>110</sup> Given its orphan drug status, Epidiolex will retain market exclusivity until September 2025,<sup>111</sup> so no generic equivalent has been approved.<sup>112</sup>

---

103. *FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy*, *supra* note 100. Epidiolex received Priority Review and Fast Track designations for Dravet syndrome, as well as Orphan Drug designation for Dravet syndrome and Lennox-Gastaut syndrome indications. *Id.*

104. This Note uses “reschedule” to refer to reassigning a controlled substance to a different schedule under the CSA.

105. Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol; Corresponding Change to Permit Requirements, 83 Fed. Reg. 48950, 48952 (Sept. 28, 2018) (to be codified at 21 C.F.R., pts 1308, 1312). Contemporaneous with this decision, the FDA also suggested moving CBD to schedule V. Letter from Admiral Brett P. Giroir, Assistant Sec’y for Health, U.S. Pub. Health Serv., to Robert W. Patterson, Acting Administrator, DEA (May 16, 2018) (on file with Regulations.gov).

106. This Note uses “deschedule” to refer to completely removing a controlled substance from the CSA.

107. *GW Pharmaceuticals PLC and Its U.S. Subsidiary Greenwich Biosciences, Inc. Announce that EPIDIOLEX® (cannabidiol) Oral Solution Has Been Descheduled and Is No Longer a Controlled Substance*, GW PHARMS. (Apr. 6, 2020), <https://web.archive.org/web/20210422024502/https://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-and-its-us-subsidiary-greenwich-1>.

108. Lindsay Slowiczek, *Epidiolex (cannabidiol)*, MEDICALNEWSTODAY, <https://www.medicalnewstoday.com/articles/epidiolex> (Dec. 8, 2021).

109. Renad Abu-Sawwa et al., *Emerging Use of Epidiolex (Cannabidiol) in Epilepsy*, 25 J. OF PEDIATRIC PHARMACOLOGY & THERAPEUTICS 485, 494 (2020).

110. FDA, *FDA Approves New Indication for Drug Containing an Active Ingredient Derived from Cannabis to Treat Seizures in Rare Genetic Disease*, <https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-rare> (July 31, 2020).

111. FDA, *Search Orphan Drug Designations and Approvals*, <https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?cfgridkey=421213> (last visited Apr. 4, 2022).

112. *Generic Epidiolex Availability*, DRUGS.COM, <https://www.drugs.com/availability/generic-epidiolex.html> (Sept. 8, 2022).

Dronabinol (brand names Marinol, Syndros) and nabilone (brand name Cesamet) are synthetic forms of THC that were developed in the 1980s. Marinol was approved by the FDA in 1985 to mitigate the side effects of chemotherapy.<sup>113</sup> The DEA placed Marinol in Schedule II during its approval process but has since rescheduled it to Schedule III.<sup>114</sup> Marinol later received seven years of exclusivity under the Orphan Drug Act in December 1992 for the treatment of anorexia in HIV/AIDS patients.<sup>115</sup> Marinol's sponsor, Unimed, has held a patent for use in patients with dementia since 1998,<sup>116</sup> but this indication has not yet gained FDA approval.<sup>117</sup> Four companies currently market generic dronabinol, with SVC Pharma first receiving generic approval in 2008.<sup>118</sup> The FDA granted marketing approval to Syndros, an oral solution form of dronabinol,<sup>119</sup> in 2016, and the DEA placed it in Schedule II.<sup>120</sup>

Eli Lilly received original approval to market Cesamet in 1985 but took it off the market in 1989 for "commercial reasons."<sup>121</sup> Valeant acquired Cesamet from Eli Lilly in 2004<sup>122</sup> and received FDA approval for use in treating chemotherapy effects and to stimulate appetite in patients with cachexia in 2005.<sup>123</sup> The DEA has categorized Cesamet as

113. *Marinol*, DRUGS.COM, <https://www.drugs.com/marinol.html> (Sept. 20, 2020).

114. INST. OF MED., MARIJUANA AND MEDICINE, ASSESSING THE SCIENCE BASE 203–04 (Janet E. Joy et al. eds., 1999); DEA, *Marijuana/Cannabis* (Apr. 2020), [https://www.dea.gov/sites/default/files/2020-06/Marijuana-Cannabis-2020\\_0.pdf](https://www.dea.gov/sites/default/files/2020-06/Marijuana-Cannabis-2020_0.pdf). The DEA made its scheduling decision before the FDA's marketing approval, so Marinol did not experience marketing delays. *Id.* at 203.

115. *Id.* at 205.

116. *Id.* The FDA has approved Phase 2 trials to study Dronabinol's effect on Alzheimer's patients with severe dementia. *Dronabinol*, ALZFORUM, <https://www.alzforum.org/therapeutics/dronabinol> (Mar. 10, 2022).

117. INST. OF MED., *supra* note 114, at 205.

118. *Generic Marinol Availability*, DRUGS.COM, <https://www.drugs.com/availability/generic-marinol.html> (Sept. 8, 2022).

119. *Syndros FDA Approval History*, DRUGS.COM, <https://www.drugs.com/history/syndros.html> (last visited Apr. 4, 2022).

120. Schedules of Controlled Substances: Placement of FDA-Approved Products of Oral Solutions Containing Dronabinol [(–)-delta-9-trans-tetrahydrocannabinol (delta-9-THC)] in Schedule II, 82 Fed. Reg. 55504, 55505 (Nov. 22, 2017) (to be codified at 21 C.F.R. pt. 1308).

121. *Valeant Returns Synthetic Cannabinoid to USA*, PHARMATIMES (May 17, 2006), [https://www.pharmatimes.com/news/valeant\\_returns\\_synthetic\\_cannabinoid\\_to\\_usa\\_996830](https://www.pharmatimes.com/news/valeant_returns_synthetic_cannabinoid_to_usa_996830). No other reasons for Cesamet's market removal are apparent from the relevant literature.

122. *Valeant Pharmaceuticals International Receives FDA Marketing Approval for Cannabinoid Cesamet (CII)*, BIOSPACE (May 16, 2006), <https://www.biospace.com/article/releases/valeant-pharmaceuticals-international-receives-fda-marketing-approval-for-cannabinoid-cesamet-tm-cii/>.

123. Nat'l Ctr for Biotech. Info., *Compound Summary: Nabilone*, PUBCHEM, <https://pubchem.ncbi.nlm.nih.gov/compound/Nabilone> (last visited Apr. 4, 2022).



a Schedule II controlled substance.<sup>124</sup> There is currently no generic version available in the United States.<sup>125</sup>

A THC and CBD-derived drug, Sativex, was developed by GW to treat spasticity associated with multiple sclerosis.<sup>126</sup> Although the drug has been approved for use in Canada and the EU, it has not been approved in the US.<sup>127</sup> But, its sponsor is currently working with the FDA on its approval for cancer pain and multiple sclerosis spasticity indications.<sup>128</sup>

### III. CANNABIS DRUG SUPPLY AND DEMAND

The underlying information about the CSA and the cannabis drug development process provides a clearer picture of cannabis innovation in the United States. The CSA adds various regulatory requirements to the drug development process, making it more difficult to bring cannabis drugs to market than small molecule drugs that do not contain Schedule I controlled substances.

Researchers have mixed conclusions about the CSA's impact on drug availability. Some have asserted that the CSA's impact on research and development is overstated and that alleged difficulties may be attributed to a lack of sophisticated players in the Schedule I drug development space.<sup>129</sup> But, the National Institutes of Health (NIH) and FDA have both characterized a substance's Schedule I status as a significant barrier to scientific research and development.<sup>130</sup> An Institute of Medicine book published in 1999 states:

---

124. *Id.*

125. *Generic Cesamet Availability*, DRUGS.COM, <https://www.drugs.com/availability/generic-cesamet.html> (Sept. 8, 2022).

126. Tracy Staton, *As Sativex Takes on Europe Bit by Bit, GW Pharma Works on FDA*, FIERCE PHARMA (Aug. 14, 2023, 11:53 AM), <https://www.fiercepharma.com/regulatory/as-sativex-takes-on-europe-bit-by-bit-gw-pharma-works-on-fda>.

127. *Id.*

128. *Id.*

129. See DV Gauvin & ZJ Zimmermann, *Schedule I Control Status Does Not Impede Legitimate Nonclinical Research in the United States*, 8 PHARM. REGUL. AFFS. 1, 3 (2019) (“[G]aining approval for legitimate and well-designed nonclinical studies that include the use of [Schedule I] substances is no more difficult than submitting the protocol for a Public Health Services Grant application (PHS) to the National Institutes of Health. . . . [T]he process of regulatory review and approval for use of [these] substances provides no more restrictions, hindrances, or difficulties than any other standard [Good Laboratory Practice] compliant sponsor-requested study preparation. The claims of government interference or hindrance in this process are more likely related to a lack of first-hand experience in this relatively small research arena.”).

130. Letter from Norman E. Sharpless, Acting Comm’r of Food & Drugs, FDA & Francis S. Collins, Dir., NIH, to Sen. Brian Schatz, Member, U.S. S. 4 (Aug. 27, 2019) (on file with Politico)

In general, pharmaceutical firms perceive scheduling to be a deterrent because it limits their ability to achieve market share for the following reasons: restricted access, physician disinclination to prescribe scheduled substances, stigma, the additional expense for abuse liability studies, and expensive delays in reaching the market due to federal and state scheduling processes.<sup>131</sup>

On the balance, the CSA has adverse effects on the supply of cannabis drugs, due to the CSA's impacts on the drug approval process, research and funding streams, patent and regulatory exclusivities, and consumer demand.

#### A. *Where the CSA and FDA Regulations Meet*

Schedule I and Schedule II substances are distinguished by whether they have a “currently accepted medical use in treatment” and whether they have an “accepted safety for use.”<sup>132</sup> As Schedule I substances by definition have no accepted medical use, their only legal use is in government-approved research projects; they cannot be dispensed and prescribed for medical purposes.<sup>133</sup> But, as discussed, some Schedule I substances have been approved by the FDA for various indications. The DEA has historically rescheduled drugs containing Schedule I substances once they gain FDA approval, because they no longer met the “no currently accepted medical use in treatment” criteria.<sup>134</sup> In fact, 10–11 percent of all prescriptions are for controlled medications.<sup>135</sup> It is worth noting that only the specific approved drugs were rescheduled in these cases and not their underlying substances. But, subsequent approvals containing those substances may be less difficult when they rely on an earlier product's marketing authorization.<sup>136</sup>

---

[hereinafter NIH & FDA Letter].

131. INST. OF MED., *supra* note 114, at 201–02. The book also notes that there is not a wealth of empirical data to back up these perceptions. *Id.* at 202.

132. 21 U.S.C. § 812(b). Medical utility and potential for abuse and dependence distinguish schedules generally. LAMPE, *supra* note 15, at 6.

133. *United States v. Oakland Cannabis Buyers' Coop.*, 532 U.S. 483, 491 (2001).

134. Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol; Corresponding Change to Permit Requirements, 83 Fed. Reg. 48950, 48951 (Sept. 28, 2018) (to be codified at 21 C.F.R., pts 1308, 1312). Marinol was rescheduled to Schedule III, INST. OF MED., *supra* note 114, Epidiolex was rescheduled to schedule V then descheduled, *GW Pharmaceuticals PLC and Its U.S. Subsidiary Greenwich Biosciences, Inc. Announce that EPIDIOLEX® (cannabidiol) Oral Solution Has Been Descheduled and Is No Longer a Controlled Substance*, *supra* note 107.

135. Dispensing of Controlled Substances to Residents at Long Term Care Facilities, 75 Fed. Reg. 37463, 37464 (June 29, 2010).

136. See Chris Morris, *FDA Clears LSD-Based Anxiety Drug for Clinical Trials*, FORTUNE (Jan. 26, 2022, 10:58 AM), <https://fortune.com/2022/01/26/fda-clears-bsd-based-drug-clinical->

Tetrahydrocannabinol is the only Schedule I substance that has been used in an approved drug, but there is a growing interest in marketing drugs containing other Schedule I substances. The psychedelic biotech company, MindMed, is interested in marketing drugs containing various psychedelics for therapeutic use.<sup>137</sup> Harvard University launched the Project on Psychedelics Law and Regulation in 2021, which focuses on promoting “safety, innovation, and equity in psychedelics research, commerce, and therapeutics.”<sup>138</sup>

When comparing the current regulatory approval processes needed to bring CBD (not a controlled substance) and THC drugs (a Schedule I substance) to market, the primary difference lies in the IND processes. Unlike CBD-derived drugs, THC-derived drugs must obtain CMC and BRM information from a DEA-registered source, approval from the DEA to use cannabis from said source, protocol registration from the DEA, and ultimately cannabis from a DEA-registered source.<sup>139</sup> THC-derived and synthetic THC drugs must also obtain study site and investigator Schedule I licenses from the DEA,<sup>140</sup> requiring submission and review of clinical and nonclinical protocols, as well as a determination of the qualifications and competency of study researchers.<sup>141</sup>

Still, access to CBD products for research remains a challenge despite its descheduled status, and there is only one CBD-derived drug on the market. This may be attributed to a variety of reasons. The DEA has adopted a position of strictly enforcing the 0.3% THC limit for hemp plant derivatives and extracts, making high-quality CBD plants for research and development purposes more difficult to procure.<sup>142</sup>

---

trials/ (indicating that clarifying the regulatory framework is one of the biggest hurdles in psychedelic drug development).

137. *Psychedelic Drugs Market Size Is Projected to Reach \$10.75 Billion by 2027*, PRNEWswire (Apr. 21, 2021, 9:00 ET), <https://www.prnewswire.com/news-releases/psychedelic-drugs-market-size-is-projected-to-reach-10-75-billion-by-2027-301273405.html>.

138. Elaine McArdle, *Reassessing Psychedelics*, HARV. L. TODAY (Jan. 31, 2022), <https://today.law.harvard.edu/reassessing-psychedelics/>. Like cannabis, the increased interest in other psychedelics has likely increased due to Oregon’s recent legalization of psilocybin for therapeutic use in 2020. *Id.* Eight cities have taken similar actions. *Id.*

139. *FDA and Cannabis: Research and Drug Approval Process*, *supra* note 41.

140. CTR. FOR DRUG EVALUATION & RSCH., OFF. OF THE CTR. DIR., MAPP 4200.1 REV1, PROCEDURES FOR REVIEW OF PROTOCOLS REFERRED BY DEA THAT USE SCHEDULE I CONTROLLED SUBSTANCES AND DRUGS 2 (2020).

141. *Id.* at 2–3.

142. Suzie Trigg et al., *Sourcing Cannabis Lawfully for CBD Consumer Products: Challenges and Opportunities*, FOOD & DRUG L. INST. (Mar. 2021), <https://www.fdli.org/2021/03/sourcing-cannabis-lawfully-for-cbd-consumer-products-and-clinical-research-challenges-and-opportunities/>.

And, the FDA is only now suggesting that real-world evidence can fill gaps in its understanding of CBD.<sup>143</sup> In addition, the legal status of synthetic CBD remains uncertain.<sup>144</sup> This Note predicts that CBD-based drug development will improve as time passes since its descheduling. On average, it takes twelve years to bring an experimental drug to market, and CBD was only descheduled in 2018.<sup>145</sup> In addition, increased federal regulation and oversight of CBD will bring needed clarity and certainty to the space,<sup>146</sup> and investment in CBD products continues to increase.<sup>147</sup>

As shown here, a substance's Schedule I status is not an absolute barrier to development, and if FDA drug approval requirements are met, the DEA will likely reschedule it. But, a drug sponsor that includes a Schedule I substance in its proposed drug must seek approval from the FDA and the DEA to even begin clinical studies. Adding requirements to the drug development process adds significant time, money, and uncertainty to an already complex and expensive process. The current state of CBD drug development further indicates that the effects of a substance having been classified as Schedule I may be long-lasting. Nevertheless, drug and biotech companies remain interested in developing drugs containing Schedule I substances, and this increased activity will likely pave the way for the approval of other drugs containing Schedule I substances.

### B. *Restrictions on Cannabis Drug Research and Development*

Restricted access to controlled substances and funding for research has a significant impact on the number of clinical studies conducted on

143. Hahn & Abernethy, *supra* note 36. The FDA published guidance in July 2020 on CBD sources, quality considerations, and percentage THC calculations. *See generally* CANNABIS AND CANNABIS-DERIVED COMPOUNDS, *supra* note 70.

144. Several non-drug products purportedly containing synthetic CBD have been flagged by the American Association of Poison Control Centers as an “emerging hazard” due to the lack of regulatory oversight in this space. *Investigation Finds Illegal Synthetic Marijuana in Vape and Edible Products Sold as CBD*, CNBC (Sept. 16, 2019, 5:00 PM), <https://www.cnbc.com/2019/09/16/investigation-finds-illegal-synthetic-marijuana-in-vape-and-edible-products-sold-as-cbd.html>. The U.S. Hemp Authority, the preeminent industry group that certifies CBD products, has maintained that it will not certify “[p]roducts with synthetic cannabinoids, biosynthetic, cannabimimetic phytochemicals in lieu of hemp-derived cannabinoids, hemp, and/or genetically engineered hemp” for use in any stage of production. U.S. HEMP AUTH., U.S. HEMP AUTHORITY® CERTIFICATION PROGRAM STANDARD V3.0 6.

145. *See supra* note 33 and accompanying text.

146. CONSUMER BRANDS ASSN., THE URGENT NEED FOR CBD CLARITY 5.

147. *CBD (Cannabidiol) Market Size to Reach USD 47.22 Billion by 2028 - Increased Demand for CBD (Cannabidiol) for Health and Wellness Purposes to Drive Market – Vantage Market Research*, *infra* note 194.

Schedule I substances and, consequently, the number of controlled medications available on the market.

Access to Schedule I substances for research is closely controlled by the DEA. Congress enacted annual production quotas for each Schedule I substance that are limited to the amount necessary to meet medical, scientific, research, and industrial needs and to prevent “overproduction, shortages, or diversions.”<sup>148</sup> Manufacturers, distributors, and dispensers of Schedule I substances must be registered, meet quotas, and keep records on each substance manufactured, received, sold, delivered, or disposed.<sup>149</sup> Production quotas are determined by trends in the national disposal rate during the preceding calendar year, the manufacturer’s production cycle and inventory position, the economic availability of raw materials, yield and stability problems, emergencies such as strikes and fires, and other factors.<sup>150</sup>

The National Institute on Drug Abuse (NIDA) Drug Supply Program contracted exclusively with the University of Mississippi from 1968–2020, making it the only legal source of cannabis for research.<sup>151</sup> Eight researchers were able to obtain NIDA cannabis in 2010, fourteen in 2019, and twenty in 2017 and 2018.<sup>152</sup> Researchers studying NIDA cannabis have described the plants as “brown, muddy garbage” that are weaker than state grown cannabis and “often moldy.”<sup>153</sup> Specialized products sold in state markets have not been available from federal sources.<sup>154</sup> But, due to “greater public interest in expanding marijuana-related research,” the DEA has recently begun to allow additional growers to supply cannabis for research purposes subject to certain evaluation criteria.<sup>155</sup> Since this change in DEA policy, the agency has

---

148. 21 U.S.C. §826(a)–(c).

149. 21 U.S.C. § 827.

150. 21 C.F.R. § 1303.22(c) (2022).

151. COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, NAT’L ACADS. OF SCIS., ENG’G, AND MED., THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH 77–78 (2017).

152. Sarah Oweremohle, *Legal Weed Is Everywhere — Unless You’re a Scientist*, POLITICO (Dec. 25, 2018, 8:00 AM), <https://www.politico.com/story/2018/12/25/legal-weed-scientists-1074188>; Sarah Oweremohle, *Why We Don’t Know Much About Pot*, POLITICO (Oct 14, 2019), <https://www.politico.com/agenda/story/2019/10/14/cannabis-medical-marijuana-research-000984/>.

153. Oweremohle, *Why We Don’t Know Much About Pot*, *supra* note 152.

154. COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, *supra* note 151, at 382–83.

155. Applications To Become Registered Under the Controlled Substances Act To

received thirty-three applications to supply NIDA with cannabis, cannabis extracts, and tetrahydrocannabinol.<sup>156</sup> Seven bulk cannabis growers have been approved to date.<sup>157</sup>

Standardization of cannabis research methodology is also needed. Methodological research challenges exist, such as standardizing dosages and smoking or ingestion techniques.<sup>158</sup> Cannabis research studies frequently use approved cannabis drugs to circumvent these issues, but they are likely to produce different results than a new drug.<sup>159</sup> Additionally, the placebo controls necessary to create a double-blind study may be ineffective due to the signature “psychoactive and vasoactive effects” of cannabis.<sup>160</sup> And, the effects of long-term cannabis use are not well studied.<sup>161</sup>

Although there have been many small-scale studies demonstrating the medicinal benefits of cannabis, government control over the supply of federally approved cannabis has thwarted efforts to conduct significant research and clinical trials.<sup>162</sup> According to Clinicaltrials.gov records, few studies have been conducted on the effects of THC and CBD, demonstrating the difficulty of submitting sufficient evidence of safety and efficacy to the FDA. One hundred forty-four clinical trials have been conducted on CBD<sup>163</sup> – 109 since CBD was descheduled<sup>164</sup> –

Manufacture Marijuana To Supply Researchers in the United States, 81 Fed. Reg. 53846, 53846 (Aug. 12, 2016) (to be codified at 21 C.F.R. pt. 1301).

156. Bulk Manufacturer of Controlled Substances Applications: Bulk Manufacturers of Marihuana, 84 Fed. Reg. 44920, 44922 (Aug. 27, 2019).

157. DOJ, *Marihuana Growers Information*, <https://www.deadiversion.usdoj.gov/drugreg/marihuana.htm> (Nov. 06, 2022).

158. COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, *supra* note 151, at 385. But, NIDA recently directed cannabis researchers to use a 5mg standard unit. Nora Volkow & Norman E. Sharpless, *Establishing 5mg of THC as the Standard Unit for Research*, NAT’L INST. ON DRUG ABUSE (May 10, 2021), <https://nida.nih.gov/about-nida/noras-blog/2021/05/establishing-5mg-thc-standard-unit-research>.

159. COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, *supra* note 151, at 386.

160. *Id.* at 386–87.

161. *Id.* at 389.

162. KM BRANCH ET AL., FACTORS AFFECTING THE REGULATORY CONTEXT OF MARIJUANA AND CANNABINOIDS IN THE WORKPLACE, PAC. NW. NAT’L LAB’Y 8-3 (2017).

163. U.S. NAT’L LIBR. OF MED., CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/results/details?cond=&term=Cannabidiolpercent09&cntry=US&state=&city=&dist=&Search=Search> (last visited Apr. 5, 2022) (finding 144 CBD clinical trials by subtracting the 34 studies using Epidiolex from search parameters).

164. U.S. NAT’L LIBR. OF MED., CLINICALTRIALS.GOV, [https://clinicaltrials.gov/ct2/results?term=Cannabidiol&cntry=US&strd\\_s=01percent2F01percent2F2018](https://clinicaltrials.gov/ct2/results?term=Cannabidiol&cntry=US&strd_s=01percent2F01percent2F2018) (last visited Apr. 5, 2022) (narrowing previous search to studies beginning after Jan. 1, 2018).

whereas only fifty-four trials have been conducted on THC.<sup>165</sup> The significant uptick in clinical trials involving CBD since its descheduling and the small number of THC studies highlights the effect of a Schedule I classification on research. Some states have authorized research and laboratory testing programs for medical cannabis,<sup>166</sup> but the DEA's restrictions on cannabis for research purposes and the FDA's clinical study requirements likely prevent these studies from being used to demonstrate safety and efficacy under current regulations.<sup>167</sup>

Additionally, the amount of public funding and support available for cannabis drug research and development is limited. Public sector support for new drug discovery is significant. Twenty-five percent of small molecule drugs containing new molecular entities approved between 2008–2017 had key late-stage research contributions from public sector research institutions, and publicly sponsored drugs are more likely to receive expedited regulatory designations.<sup>168</sup> Public sector research institutions also contribute significantly to drug development beginning in basic research and preclinical developments stages,<sup>169</sup> and these institutions could risk losing federal grants if they conduct unapproved or state-level cannabis research.<sup>170</sup>

The cost of bringing a drug to market has been estimated in the range of \$985 million to \$2.6 billion,<sup>171</sup> and these estimates do not account for the cost of complying with DEA regulations for Schedule

---

165. U.S. NAT'L LIBR. OF MED., CLINICALTRIALS.GOV, <https://bit.ly/38omO9v> (last visited Apr. 5, 2022) (searching for "Tetrahydrocannabinol" clinical trials located in the United States; then manually saving searches that did not involve Dronabinol, Marinol, or Syndros, as these drugs are not Schedule I substances).

166. Several states including Arizona, ARIZ. REV. STAT. Ann. § 36-2812 (2021), California, CAL. HEALTH & SAFETY CODE § 11362.9 (West 2019), and Florida, FLA. STAT. Ann. § 1004.4351 (West 2021), have statutory provisions funding the scientific study of cannabis.

167. *But see* discussion *infra* notes 211–16.

168. Rahul K. Nayak et al., *Public Sector Financial Support for Late Stage Discovery of New Drugs in the United States: Cohort Study*, 367 *BMJ* 15766, 15766 (2019).

169. *Id.*

170. Owen Daugherty, *Risk of Losing Federal Funding Reason Why Medical Marijuana Research Won't Happen*, THE LANTERN (Aug. 23, 2017), <https://www.thelantern.com/2017/08/risk-of-losing-federal-funding-reason-why-medical-marijuana-research-wont-happen/>. However, recent legislation will likely allow registered public universities to conduct cannabis research for purposes of "drug development or subsequent commercial production." Medical Marijuana and Cannabidiol Research Expansion Act, Pub. L. No. 117-215, §201, 136 Stat. 2264 (2022) (codified as amended in 21 U.S.C. §823).

171. *See* Oliver J. Wouters et al., *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 *JAMA* 844, 844 (2020) (\$985 million); Rick Mullin, *Tufts Study Finds Big Rise in Cost of Drug Development*, C&EN (Nov. 20, 2014) (\$2.6 billion), <https://cen.acs.org/articles/92/web/2014/11/Tufts-Study-Finds-Big-Rise.html>.

I drugs.<sup>172</sup> The NIH is one of the main public cannabis research funders, providing \$111.3 million for 285 projects in 2015 and \$189 million for 408 projects in 2019.<sup>173</sup> But, these investments make up only 0.5 percent of NIH's overall research budget.<sup>174</sup> In addition, NIDA has prioritized funding studies on the negative health effects and behavioral consequences of cannabis, rather than health benefits.<sup>175</sup> In 2015, NIDA made up 59.3 percent of NIH cannabis research spending, but only 16.5 percent of this spending went to research investigating cannabis's therapeutic properties.<sup>176</sup> The Center for Medicinal Cannabis Research at the University of California, San Diego also provides grants for cannabis research, funded by sales of state recreational cannabis, but grants are competitive at a 12 percent funding rate.<sup>177</sup>

As a result of the limited public support and funding available for cannabis research, pharmaceutical and biotech companies have taken the lead on cannabis drug research and development. Private funding for cannabis research remains available, although companies selling cannabis cannot trade on the New York Stock Exchange due to its federal illegality.<sup>178</sup> Still, big pharmaceutical companies have begun to dedicate funds to cannabis-derived drug development,<sup>179</sup> and many smaller biotech companies raise funds through venture capital, mergers and acquisitions activity, real estate investment trusts, and from tech and celebrity investors.<sup>180</sup>

---

172. See COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, *supra* note 151, at 381 (clarifying that sponsors must pay for the cost of DEA's security requirements surrounding research cannabis at testing facilities).

173. Ziva D. Cooper et al., *Challenges for Clinical Cannabis and Cannabinoid Research in the United States*, 58 J. OF THE NAT'L CANCER INST. MONOGRAPH 114, 119 (2021).

174. *Id.*

175. COMM. ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REV. & RSCH. AGENDA, *supra* note 145, at 384.

176. *Id.*

177. Cooper et al., *supra* note 173.

178. Eric Volkman, *Marijuana Stocks Not Trade on the Major Stock Exchanges?*, THE MOTLEY FOOL (Nov. 25, 2020, 2:00 PM), <https://www.fool.com/investing/2020/11/25/why-do-so-many-marijuana-stocks-not-trade-on-the-m/>. But, several ancillary cannabis companies and biopharma companies working with cannabis can and do trade on the US stock market. Nathan Reiff, *Top Marijuana Stocks on the Nasdaq for March 2022*, INVESTOPEDIA, <https://www.investopedia.com/investing/top-marijuana-stocks-nasdaq/> (Aug. 31, 2022).

179. See discussion *supra* Section III.A.

180. Brett Relander, *Funding Platforms for Marijuana Startups*, INVESTOPEDIA, <https://www.investopedia.com/articles/investing/030515/funding-platforms-emerging-marijuana-startups.asp> (Dec. 31, 2021); Michael Regan, *Cannabis Companies with Specific Plans for New Funding Find Success at Raising Capital*, MJBIZ, <https://mjbizdaily.com/success-in-cannabis-fundraising-boosted-by-specific-plans-for-the-capital/> (Dec 17, 2021).



### C. *Cannabis Drug Exclusivities*

Drug exclusivities are vital to the pharmaceutical industry's willingness to invest in new drug research and development. The uncertainty and high cost of creating a successful drug all but requires the incentive of monopoly profits to recoup the losses for failed drug development efforts. A survey of pharmaceutical companies showed that they find patents "extremely" important, and experts have estimated that "65 percent of commercially introduced inventions in the pharmaceutical industry would not have been introduced without patents."<sup>181</sup>

The CSA does not bar patent eligibility for Schedule I drugs,<sup>182</sup> and regulatory exclusivities are available for newly approved cannabis drugs, further incentivizing innovation.<sup>183</sup> The FDA's exclusivities prevent generic equivalents to brand name drugs from entering the market for a certain amount of time, which allows brand name drug sponsors to enjoy monopoly profits that offset the cost of research and development. Use patents are available for cannabis drugs,<sup>184</sup> as are patents for certain types of cannabis plants, commonly known as strains.<sup>185</sup> Plant patents grant exclusive rights over clones of the patented plant. So far, twelve strains have been patented and registered with the International Union for the Protection of New Varieties of Plants.<sup>186</sup>

Around three hundred upstream-midstream-downstream utility patents have been filed worldwide for cannabis innovations—26 percent of which were filed in the United States.<sup>187</sup> Certain companies

---

181. Ian Cockburn & Genia Long, *The Importance of Patents to Innovation: Updated Cross-Industry Comparisons with Biopharmaceuticals*, 25 EXPERT OP. ON THERAPEUTIC PATS. 739, 740 (2015).

182. CONG. RSCH. SERV., R44643, THE HATCH-WAXMAN ACT: A PRIMER 9 (2016) (explaining that new drugs that qualify as a new chemical entity (NCE) enjoy a five-year regulatory exclusivity period under the Hatch-Waxman Act).

183. See, e.g., *supra* note 103 (discussing Epidiolex's exclusivities).

184. *Generic Epidiolex Availability*, *supra* note 112.

185. See Nick Jokomes, *Predicting Cannabis Strain Effects from THC and CBD Levels*, LEAFLY (Mar. 23, 2017), <https://www.leafly.com/news/science-tech/predicting-cannabis-strain-effects-from-thc-cbd-levels> (July 28, 2020) (generally discussing various effects of cannabis strains).

186. See Tamara Fraizer, *Twelve Cannabis Plant Patents and Counting*, NAT. L. REV. (Jan. 2, 2021), <https://www.natlawreview.com/article/twelve-cannabis-plant-patents-and-counting> ("By law, a US plant patent constitutes registration under the International Union for the Protection of New Varieties of Plants.").

187. Joseph Wyse & Gilad Luria, *Trends in Intellectual Property Rights Protection for Medical Cannabis and Related Products*, 3 J. OF CANNABIS RSCH., 1, 6 fig. 1 (2021). "Upstream" refers to technologies used in cannabis plant cultivation and breeding. *Id.* at 5. "Midstream" refers to

hold multiple patents, with GW Pharmaceuticals and GW Research Ltd. holding over seventy-five.<sup>188</sup> Specifically, many of GW’s Epidiolex patents are use patents for the treatment of epilepsy.<sup>189</sup> GW also holds patents for “[p]rocesses and apparatus[es] for extraction of active substances and enriched extracts from natural products,”<sup>190</sup> which could be used to manufacture other cannabis-derived drugs. It should be noted that although the CSA does not negatively affect cannabis exclusivities, if a particular drug never comes to market or a patented indication is not approved, exclusivities alone may not provide the returns necessary to offset the costs of research and development.<sup>191</sup>

#### D. Market Demand for Cannabis-Derived Drugs

Consumer demand for medical cannabis products is high and rising, and future cannabis drugs are well-positioned to succeed. The global medical cannabis market was valued at \$6.82 billion in 2020 and is projected to reach \$53.88 billion by 2030.<sup>192</sup> The chronic pain segment of the market was the largest during the measured periods.<sup>193</sup> Global CBD product sales were projected at \$4.9 billion in 2021 and are projected to reach \$47.22 billion by 2028.<sup>194</sup>

Epidiolex’s market success suggests that cannabis drugs have a profitable future. Epidiolex sales increased by over 72 percent in 2020.<sup>195</sup> GW Pharmaceuticals earned \$526 million in total product sales

---

technologies used in cannabis extraction, purification, and separation. *Id.* at 8. “Downstream” refers to technologies used to create cannabis compounds intended to treat various medical conditions. *Id.*

188. *Id.* at 13 fig. 5.

189. *Generic Epidiolex Availability*, *supra* note 112.

190. *Id.*

191. *See, e.g., supra* note 171 and accompanying text.

192. Smita Nerkar & Onkar Sumant, *Medical Cannabis Market by Product Type (Buds/Marijuana Flower and Cannabis Extracts), Application (Chronic Pain, Mental Disorders, Cancer, and Others), and End User (Pharmaceutical and Research & Development Centers): Global Opportunity Analysis and Industry Forecast, 2021–2030*, ALLIED MKT. RSCH. (Oct. 2021), <https://www.alliedmarketresearch.com/medical-cannabis-market-A14250>.

193. *Id.*

194. *CBD (Cannabidiol) Market Size to Reach USD 47.22 Billion by 2028 - Increased Demand for CBD (Cannabidiol) for Health and Wellness Purposes to Drive Market – Vantage Market Research*, GLOBALNEWSWIRE (Feb. 8, 2022, 2:40 PM), <https://www.globenewswire.com/en/news-release/2022/02/08/2380516/0/en/CBD-Cannabidiol-Market-Size-to-Rreach-USD-47-22-Billion-by-2028-Increased-Demand-for-CBD-Cannabidiol-for-Health-and-Wellness-Purposes-to-Drive-Market-Vantage-Market-Research.html>. Many CBD products make health and wellness claims, suggesting that there would be robust consumer demand for medical CBD. *Id.*

195. Eric Volkman, *Jazz Pharmaceuticals’ Acquisition of GW Pharmaceuticals Closes*, THE MOTLEY FOOL (May 5, 2021, 4:54 PM), <https://www.fool.com/investing/2021/05/05/jazz-pharmaceuticals-acquisition-of-gw-pharmaceuti/>. Overall prescription drug spending in the US

in that year, with \$510 million of these profits (97 percent) coming from Epidiolex alone.<sup>196</sup> And, companies that have pioneered cannabis-derived drug research and development are being acquired for billions. Jazz Pharmaceuticals acquired GW for \$7.6 billion in 2021, with Epidiolex being a particular draw as a “potential blockbuster drug.”<sup>197</sup> GW’s arsenal of cannabis patents also likely contributed significantly to its valuation.<sup>198</sup> Also in 2021, Pfizer acquired Arena Pharmaceuticals for \$6.7 billion, mostly for its pipeline dedicated to cannabinoid-type therapeutics.<sup>199</sup>

A final consideration on consumer demand is the difficulty of patients to access controlled medications, especially Schedule II medications. Schedule II medications “must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice.”<sup>200</sup> Prescription refills of Schedule II medications are not permitted,<sup>201</sup> and the federal government requires that prescribing practitioners “see their patients in an appropriate time and manner . . . to thereby minimize the likelihood that patients will abuse, or become addicted to, the controlled substances.”<sup>202</sup> Requiring patients to see their health care provider each time they need a drug can be a significant barrier to access for low-income individuals with minimal or no insurance coverage. Some states have imposed additional restrictions on the number of days a Schedule II medication

---

only increased by a “moderate” rate of 4.9 percent in 2020, largely driven by increased utilization. Eric M. Tichy et al., *National Trends in Prescription Drug Expenditures and Projections for 2021*, 78 AM. J. OF HEALTH-SYSTEM PHARM. 1294, 1294 (2021).

196. *GW Pharmaceuticals Provides Preliminary Fourth Quarter and Full-Year 2020 Net Product Sales Results and 2021 Program Milestones*, GLOBALNEWSWIRE (Jan. 11, 2021, 7:00 PM), <https://www.globenewswire.com/news-release/2021/01/11/2156125/26153/en/GW-Pharmaceuticals-Provides-Preliminary-Fourth-Quarter-and-Full-Year-2020-Net-Product-Sales-Results-and-2021-Program-Milestones.html>.

197. Volkman, *supra* note 195.

198. *See supra* note 188 and accompanying text.

199. Dario Sabaghi, *Pfizer Bets on Medical Cannabis with \$6.7 Billion Acquisition*, FORBES (Dec. 20, 2021, 8:33 AM), <https://www.forbes.com/sites/dariosabaghi/2021/12/20/pfizer-to-enter-the-medical-cannabis-industry-with-67-billion-acquisition/?sh=695080536072>. M&A Activity among Canadian pharmaceutical companies also reflect this trend. *See id.* (citing J&J Toronto’s acquisition of R&D company Avicanna, and Tilray’s agreement to develop and distribute Novartis AG medical cannabis products).

200. 21 C.F.R. § 1306.04(a) (2022).

201. 21 C.F.R. § 1306.12(a) (2022).

202. Issuance of Multiple Prescriptions for Schedule II Controlled Substances, 72 Fed. Reg. 64921, 64928 (Nov. 19, 2007) (to be codified at 21 C.F.R. pt. 1306).

may be dispensed after the date of prescription<sup>203</sup> and on the amount of a Schedule II medication that may be prescribed at one time.<sup>204</sup>

The specific effects of the CSA on cannabis drug supply and demand are mixed and nuanced. Although the CSA does not have a notable effect on consumer demand for cannabis drugs or available exclusivities, it does create barriers to research and development. The law restricts the supply of cannabis plant material and requires drug sponsors to obtain Schedule I licenses before conducting clinical studies, limits public sector support for research, and impedes patient access to approved cannabis drugs. On the whole, the CSA disincentivizes cannabis drug production, so lawmakers and agencies must make changes to the drug development process if they wish to incentivize innovation in this space.

#### IV. POLICY RECOMMENDATIONS

Although much can be said about the potential effects of rescheduling or descheduling cannabis on cannabis drug development,<sup>205</sup> Congress and federal agencies can act under the current scheduling regime to pave the way for cannabis drug innovation. The biggest barriers are the restriction of access to cannabis products, limits on research funding, and the arduous process of obtaining Schedule I research licenses. But, some barriers to drug development remain after a substance has been removed from Schedule I that could be alleviated by increased agency clarity.

At the IND stage, the FDA could permit researchers to gather real-world evidence (RWE) from the use of state-legal cannabis products to inform its considerations of cannabis drug safety and efficacy. The FDA released draft guidance in 2021<sup>206</sup> of how the agency proposes to use RWE in its decisions of “whether to approve the drug, what the drug’s indication(s) should be, and what safety protocols (if any) are necessary to ensure safe use of the product.”<sup>207</sup> The FDA and DEA should also

203. See *State-By-State Prescribing Laws*, AM. ACAD. OF FAM. PHYSICIANS (2011) (requiring that Schedule II medications must be dispensed within seven days in Illinois).

204. See *id.* (requiring that a maximum 7-day supply of Schedule II medications may be dispensed at one time in Washington, D.C.).

205. This Note refrains from advocating about whether or how cannabis should be rescheduled or descheduled.

206. See generally FDA, CONSIDERATIONS FOR THE USE OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR DRUG AND BIOLOGICAL PRODUCTS (2021).

207. John Concato & M. Khair ElZarrad, *FDA Issues Draft Guidances on Real-World*

give weight to prior approved Schedule I license grants and IND applications in their future considerations of drugs containing the same or similar substances. Such a policy is logical, would pave the way for follow-on Schedule I drug innovation, and especially incentivize synthetic cannabis drug development, which primarily faces Schedule I licensing as a barrier to development.

To increase the available supply of quality cannabis for research, NIDA should continue to approve cannabis grower applications, particularly for sophisticated companies that can supply high-quality plant material and extracts. The FDA and DEA could also allow state-licensed growers to provide cannabis for federal research if they comply with the CSA's security and reporting requirements.<sup>208</sup> Agencies could also consider permitting state-licensed cannabis researchers to conduct clinical trials. These research facilities operate in many medical cannabis states to test products for quality control purposes, already own testing equipment, and would likely be capable of meeting the FDA's laboratory standards.<sup>209</sup> Finally, the DEA should adjust its annual cannabis production quota determinations to reflect the need for various strains, product types, and concentrations in drug research.

To further incentivize research, agencies could provide additional funding for companies engaging in the uncertain area of cannabis drug development. NIH should expand the number and types of grants available to cannabis researchers and prioritize studies of cannabis for therapeutic purposes. The Patent and Trademark Office should continue to permit robust cannabis patent protections, and the FDA should continue to make various exclusivities and expedited approval options available for cannabis drugs with approved indications for rare and hard-to-treat conditions.

---

*Evidence, Prepares to Publish More in Future*, FDA, <https://www.fda.gov/drugs/news-events-human-drugs/fda-issues-draft-guidances-real-world-evidence-prepares-publish-more-future> (Jan. 31, 2022). Proposed sources of RWE include “data from electronic health records (EHRs); medical claims data, data from product and disease registries; patient-generated data (including data from in-home-use settings); and data gathered from other sources that can inform on health status, such as mobile devices.” FDA, DATA STANDARDS FOR DRUG AND BIOLOGICAL PRODUCT SUBMISSIONS CONTAINING REAL-WORLD DATA GUIDANCE FOR INDUSTRY 2 (2021).

208. A provision of the Infrastructure Investment and Jobs Act directs the Department of Transportation and HHS to use state-licensed cannabis products to study cannabis-impaired driving. Infrastructure Investment and Jobs Act, Pub. L. 117-58, 135 Stat. 880–81 (2021).

209. Nancy Maddox, *Into the Weeds: Cannabis Testing and Public Health Labs*, ASS'N OF PUB. HEALTH LABS (2017), <https://www.aphl.org/aboutAPHL/publications/lab-matters/Pages/into-the-weeds.aspx>.

The DEA could also assist approved THC drug sponsors with the rescheduling process and encourage CBD drug development by making three policy changes.<sup>210</sup> First, the DEA should provide a standardized timeline and process for rescheduling or descheduling drugs derived from Schedule I substances. Second, the DEA should consider prior rescheduling decisions when evaluating future rescheduling decisions involving the same substance, and make scheduling decisions prior to final FDA approval, as it did with Marinol, to avoid marketing delays. Finally, the DEA should immediately lift or adjust relevant restrictions on supply, manufacturing, distribution, and dispensing once a product has been rescheduled or descheduled. Any policy change implemented by the DEA should be communicated with the FDA (and USDA as appropriate) to avoid confusion with implementation.

The legal and regulatory landscape governing cannabis drug development is continually shifting. President Biden signed the Medical Marijuana and Cannabidiol Research Expansion Act into law on December 2, 2022.<sup>211</sup> The Act revises the cannabis research application process,<sup>212</sup> allows federally funded universities to conduct cannabis studies,<sup>213</sup> requires the DEA to register manufacturers and distributors of FDA-approved cannabis drug products,<sup>214</sup> and directs the DEA to assess the supply of cannabis required for research purposes.<sup>215</sup> It also allows physicians to discuss the potential harms and benefits of cannabis with patients.<sup>216</sup> As of this Note's publication, it is unclear how the Act will impact cannabis drug innovation and no relevant regulations have been promulgated.

Further studies would help quantify the effects of the Act, such as a study of the effect of additional approved cannabis growers on the number of clinical trials, submitted and approved INDs, and approved NDAs. Other useful research could include a cost analysis of DEA

---

210. Once a substance has an accepted medical use, it should no longer be considered a Schedule I drug. *See supra* note 134 and accompanying text. And, CBD is still experiencing growing pains despite being descheduled in 2018. *See discussion supra* Part III.A.1 (noting that the regulatory process has become simplified but only one CBD drug has been approved by FDA).

211. Pub. L. No. 117-215, 136 Stat. 2257 (2022) (codified as amended in scattered sections of 21 U.S.C.).

212. §§ 101–103, 136 Stat. at 2258–63.

213. § 201, 136 Stat. at 2264.

214. § 202, 136 Stat. at 2264–65.

215. § 104, 136 Stat. at 2263–4.

216. § 301, 136 Stat. at 2265.

compliance on the research and development process for each CSA schedule, a study of CBD product development outside the drug space, and an evaluation of whether barriers to cannabis development are reflected in efforts to market other drugs derived from Schedule I substances, such as LSD and MDMA.

#### CONCLUSION

The market for cannabis drugs is ripe for the taking, and the biggest barrier for developers is navigating the various regulatory complexities. Although some may assume that cannabis must be rescheduled to pave the way for pharmaceutical and biotech companies to enter the space, new cannabis drug development is possible under the current framework. In such a dynamic market, agencies and private companies might tend to be cautious about establishing and adhering to procedures that are subject to change, but there are patients ready for cannabis drugs and companies that are bold enough to take the risk and innovate first. The only question is who will move next.